

Bioinformatic Analysis of Diagnosis, Targeted Therapeutic Values and Potential Regulatory Network of FOXF1 in Ovarian Cancer

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Research

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Abstract

Background: FOXF1 acts a crucial part to tumor initiation and progression. In this study, we aimed to analyzed FOXF1 in ovarian cancer from different databases which showed diagnosis and targeted therapeutic values.

Results: The expression of FOXF1 in ovarian cancer tissue was markedly lower than that in normal tissue. Among different tumor subgroups, FOXF1 expression was conspicuously lower in higher grade stage. Additionally, FOXF1 expression and genetic variations were significantly correlated with various immune infiltrating cells. Altogether, 2594 co-expressed genes evidently pertinent to FOXF1. These genes were correlated with cell adhesion, NADH dehydrogenase complex and cytokine binding in results of enrichment analysis. In addition, FOXF1 was associated with gene networks regulated by PRKG1, miR-151, and SRF respectively. CMap analysis screened several potential small molecules for ovarian cancer treatment.

Conclusions: FOXF1 has been shown to be a vital biomarker for the diagnosis of ovarian cancer and the immune infiltrating levels. The small molecules screened here supply rationale for new drug development for ovarian cancer.

Background

As one of the most common tumors in women, ovarian cancer is characterized with high morbidity and mortality[1]. Ovarian cancer has a higher mortality rate than cervical cancer in malignant gynecological tumors. Ovarian cancer alone kills some 180,000 people each year[2]. Due to the inconspicuous early symptoms and a lack of reliable early screening modalities, about 70% of ovarian cancer patients are diagnosed with advanced stages[3]. Although ovarian cancer can be treated with surgery combined with chemotherapy drugs, the five-year survival rate hovers around 30 percent due to frequent recurrence and metastasis[4, 5]. Therefore, more new biomarkers need to be found to improve the early diagnosis of ovarian cancer, so as to improve the efficiency of individualized treatment of patients. In addition to early diagnosis, molecular targeted therapy of ovarian cancer also faces great challenges[6]. Hence, it is urgent to explore regulatory network and therapeutic values of key genes related to the occurrence and metastasis of ovarian cancer.

FOX family genes are play important roles in regulating transcription and translation process of various genes by encoding proteins. They play important roles in cell proliferation, differentiation, apoptosis, organ development, aging, regulation of metabolic balance and tumorigenesis[7]. In recent years, the FOX gene family has been shown to consist of 19 subfamilies (FOXA-FOXs) and 50 genes[8]. Among these genes, FOXF1 participates in development of several types of cancer via binding to the promoter and activating the expression of several cancer-specific genes[9–11]. The role of FOXF1 in tumor progression has attracted increasing attention. In colorectal cancer (CRC), FOXF1 could transcriptionally activating SNAI1 to induce epithelial-mesenchymal transition[9]. Highly expressed FOXF1 could also induce tumor suppressor and regulate cell cycle of Non-Small-Cell lung cancer (NSCLC)[12]. FOXF1 has also been reported to participate in regulating drug resistance of several kinds of cancer. In CRC, upregulation of FOXF1 might inhibited VEGFA attenuated angiogenesis and bevacizumab resistance[13]. Cisplatin susceptibility of NSCLC cells could also be influenced by FOXF1[14]. Mutation, deficiency or inactivation of FOXF1 was also associated with prognosis of patients with cancer. Some researchers found FOXF1 re3950627 might be a promising prognostic marker in gastric cancer (GC) patients[15]. Loss of FOXF1 expression was also linked to poor overall survival of patients with hepatocellular carcinoma (HCC)[16]. These findings imply that the functional role of FOXF1 might be cancer-specific. However, there are few studies carried out on FOXF1 in ovarian cancer, and few researchers draw on any systematic research into the specific functional mechanism of FOXF1 on ovarian cancer progression.

In this study, a comprehensive assessment was performed on the FOXF1 gene expression profile and its clinical data through various online websites and publicly available databases. We determined the expression and variations of FOXF1 and its association with immune cell infiltrating in ovarian cancer. The molecular mechanisms by which FOXF1 is involved in tumor infiltration were further investigated. In addition, we also studied the potential regulatory network and potential targeted drugs to FOXF1 in ovarian cancer. This study provides a new direction for the role of FOXF1 in ovarian cancer and provides a trustworthy groundwork for FOXF1 as diagnosis biomarker and a target for therapy.

Results

Expression analysis of FOXF1 in various cancers and ovarian cancer

A variety of databases were utilized to analyze the expression of FOXF1 in different cancers. The analysis results in the Oncomine database demonstrated that FOXF1 was up-regulated in esophageal cancer, lymphatic cancer, pancreatic cancer, sarcoma, while down-regulated in bladder cancer, kidney cancer, lung cancer and ovarian cancer (Fig. 1a). Gene expression Profiling Interactive Analysis (GEPIA) analysis results displayed that the expression of FOXF1 in most types of cancer tissues was significantly lower than that in corresponding normal tissues, while the expression of FOXF1 in pancreatic cancer was prominently higher than that in corresponding normal tissues (Fig. 1b). The analysis results of TIMER website in Fig. 1c illustrated that the expression of FOXF1 was lower in most types of cancer tissues, whereas remarkably highly expressed in ovarian cancer, squamous cell carcinoma of head and neck and kidney cancer.

The expression of FOXF1 in ovarian cancer was further analyzed on the Oncomine online website. The results exhibited that the expression of FOXF1 in ovarian cancer was notably reduced compared with that in adjacent tissue (Fig. 2a), which was further confirmed with the dataset of GSE66957 (Fig. 2b). The above results signified that the expression of FOXF1 was down-regulated in most cancers including ovarian cancer.

Correlation between FOXF1 expression and clinical features of ovarian cancer

The correlation between FOXF1 expression and various clinical features of ovarian cancer was analyzed using UALCAN. The expression of FOXF1 was not associated with age, stage and TP53 mutation (Fig. 3a, 3c, 3e). However, the expression of FOXF1 was higher in Caucasian (Fig. 3b). Moreover, the expression of FOXF1 had decreased trend with the grade progression of tumor (Fig. 3d).

Correlation analysis between FOXF1 expression and 8 kinds of immune infiltrates

The TIMER database was implemented to analyze the correlation between FOXF1 expression tumor purity and 8 kinds of immune infiltrates (B cells, CD8 + T cells, monocyte cells, T cell regulatory (Tregs), macrophage M1, macrophage M2, neutrophils, and NK cells). The results indicated that the expression of FOXF1 in ovarian cancer had a notable negative correlation with tumor purity (Fig. 4a). About immune infiltrates, the expression of FOXF1 had a notable positive correlation with infiltration of B cells, CD8 + T cells, monocyte cells, Tregs, macrophage M1, macrophage M2, neutrophils, and NK cells (Fig. 4b-4i).

Correlation analysis between copy number variation (CNV) of FOXF1 and immune infiltrates

Genetic variations of FOXF1 were analyzed using CBioPortal database. FOXF1 displayed low incidence rate (4%) of genetic variations. Most genetic variations in FOXF1 were deep deletion (Fig. 5a). For immune infiltrate, the degree of immune cell infiltration of immune cells including B cells, CD8 + T cells, Tregs and macrophage M1 was significantly increased in the FOXF1 deep deletion group (Fig. 5b). These results suggest CNV of FOXF1 was associated with immune infiltrates.

Analysis of genes co-expressed with FOXF1 in ovarian cancer

Subsequently, genes related to FOXF1 expression in TCGA-OV dataset were explored by LinkedOmics. From the volcano map in Fig. 6a, it was exhibited that 2583 genes (red dots) were dramatically positively correlated with FOXF1 expression, and 1011 genes (green dots) were remarkably negatively correlated with FOXF1 expression, which pointed out that FOXF1 had extensive effects in ovarian cancer at the transcriptional level. The top 50 genes that were notably positively correlated or negatively correlated with the FOXF1 gene were selected to draw heat maps (Fig. 6b, 6c), wherein the expression of ISM1, COL5A2, and CRISPLD1 was most prominently positively correlated with the expression of FOXF1 (Fig. 6d, 6f).

Enrichment analysis of FOXF1 functional networks in ovarian cancer

Gene set enrichment analysis (GSEA) was conducted on FOXF1-related genes to analyze enriched Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. FOXF1 was found to be mainly related to biological process (BPs) such as cell adhesion mediated by integrin and RNA modification (Fig. 7a), Cellular component (CC) such as NADH dehydrogenase complex and MHC protein complex (Fig. 7b), and Molecular function (MF) such as cytokine binding and rRNA binding (Fig. 7c). Moreover, KEGG pathway analysis denoted that FOXF1 was mainly enriched in the pathways involved in DNA replication and ECM-receptor interaction (Fig. 7d). These pathways might be associated with tumor progression and involved in ovarian cancer tumorigenesis.

FOXF1 networks of kinase, miRNA or transcription factor target in ovarian cancer

To explore the regulatory network of kinase, miRNA, or transcription factor targets of FOXF1 gene in ovarian cancer, GSEA was conducted. The top 5 genes of kinases, miRNAs, or transcription factor targets were listed in Table 1. PRKG1, miR-151 and SRF were hub genes which were related to FOXF1. Hence, GeneMANIA was implemented to obtain the networks of kinase PRKG1, miR-151 and SRF. The gene set of PRKG1 mainly participated in the regulation of calcium ion transport (Fig. 8a). miR-151 mainly participated in the regulation of cell division (Fig. 8b). The transcription factor SRF mainly participated in the regulation of homotypic cell-cell adhesion and pri-miRNA transcription by RNA polymerase II (Fig. 8c).

Table 1
FOXF1 networks of kinase, miRNA and transcription factor targets in ovarian cancer (LinkedOmics)

Enriched Category	Geneset	leadingEdgeNum	FDR
Kinase Target	Kinase_PRKG1	10	0.015
	Kinase_CDK7	4	0.017
	Kinase_ATR	25	0.022
	Kinase_ZAP70	8	0.087
	Kinase_PRKCG	15	0.092
miRNA Target	AGTCTAG, MIR-151	4	0.005
	CTCCAAG, MIR-432	17	0.051
	AGCATTA, MIR-155	30	0.131
	ATACCTC, MIR-202	31	0.135
	TACGGGT, MIR-99A, MIR-100, MIR-99B	7	0.136
Transcription Factor Target	V\$SRF_01	21	0.000
	CCAWWNAAGG_V\$SRF_Q4	33	0.001
	V\$COREBINDINGFACTOR_Q6	90	0.016
	V\$AML_Q6	72	0.017
	V\$RP58_01	61	0.018

LeadingEdgeNum: the number of leading-edge genes; FDR: false discovery rate from Benjamini and Hochberg from gene set enrichment analysis (GSEA); V\$: transcription factor (TF) annotation found in Molecular Signatures Database (MSigDB)

Screening of potential therapeutic drugs for ovarian cancer

In order to screen potential therapeutic drugs which were related to FOXF1 and ovarian cancer, FOXF1 related differentially expressed genes (DEGs) were screened (Fig. 9a, 9b). After this, DEGs were analyzed in Connectivity Map (CMap). Thereafter, connectivity scores of the results were ranked. Smaller score denoted for more significant reversal effect of drug molecules on cancer. Lastly, top 10 small molecules were selected for ovarian cancer treatment (Table 2).

Table 2
Overview of targeted drugs predicted by CMap

Drug name	Cell line	n	Target name	C S
PS-178990	HT29	2	AR	-
veliparib	HELA	2	PARP1,PARP2	-
dacinostat	NEU	2	HDAC1,HDAC2,HDAC3,HDAC4,HDAC5,HDAC6,HDAC7,HDAC8,HDAC9	-
tadalafil	THP1	2	PDE5A,PDE11A	-
PD-0325901	HS578T	2	MAP2K1,MAP2K2	-
AZD-1981	MCF7	3	PTGDR2	-
promazine	A375	5	CHRM5,DRD2,ADRA1A,ADRA1B,ADRA1D,CHRM1,CHRM2,CHRM3,CHRM4,DRD1,DRD3,DRD4,HRH1,HTR2A,HTR2C	-
prazosin	A375	3	ADRA1A,ADRA1B,ADRA1D,ADRA2A,ADRA2B,ADRA2C,CDK1,KCNH2,KCNH6,KCNH7	-
orphenadrine	PC3	2	CYP2B6,GRIN1,GRIN2D,GRIN3A,GRIN3B,HRH1,SCN10A,SLC6A2	-
estropipate	SKB	2	ESR1,ESR2	-

Discussion

FOXF1 belongs to a multigene family of FOX that is abnormal expression in various malignant tumors and is involved in various biological processes, such as proliferation, differentiation, metabolic balance of tumor cells. However, the role of FOXF1 in malignant tumors, especially ovarian cancer, have rarely been studied. In this study, we first investigated the expression of FOXF1 in all kinds of cancer including ovarian cancer. The sub-group analysis of multiple clinic pathological features also showed a close connection between FOXF1 and ovarian cancer in the present study. The correlation between FOXF1 and immune infiltrates has also been analyzed to gain more detailed insights into the underlying functions of FOXF1 in tumor immune. In addition, genes co-expressed and potential targeted drugs with FOXF1 in ovarian cancer were analyzed to explore the regulatory effect and targeted therapeutic values of FOXF1 in ovarian cancer.

Early screening methods and biomarkers were lacking in the early diagnosis of ovarian cancer. Hence, it is urgent to find more biomarkers to improve early diagnosis. Numerous reports have shown that FOXF1 was abnormal expression in several kind of tumor which were consistent with the results in our study[13, 18]. FOXF1 expression is also significantly associated with the malignant phenotypes of CRC and papillary thyroid cancer (PTC)[13, 18]. These results suggest FOXF1 exists potential diagnosis values in these cancers. The expression of FOXF1 in ovarian cancer has been found notably reduced compared with that in adjacent tissue in our study. The sub-group analysis also showed the expression of FOXF1 decreased conspicuously with the grade progression of tumor. We suggest that FOXF1 deserves further clinical validation as prognostic factor.

In addition to early diagnosis, effective treatment is also essential to improve the prognosis of cancer patients. Immune-related mechanisms have been reported to be involved in occurrence and development of ovarian cancer[19, 20]. Therefore, immunotherapy strategy is also considered to be a promising direction in the clinical treatment of ovarian cancer. Therefore, this study also illustrates a significant association between FOXF1 expression and multiple tumor-infiltrating immune cells in ovarian cancer. The expression of FOXF1 had a notable negative correlation with infiltration of B cells, CD8 + T cells, monocyte cells, Tregs, macrophage M1, macrophage M2, neutrophils, and NK cells in our study. Overexpression of FOXF1 could change the level of monocyte chemoattractant protein 1 (MCP-1) in FOXF1 + mice[21]. MCP-1 has specific chemokine activation to monocytes and macrophages. FOXF1 has also been proved that it was correlated with high macrophage infiltration in glioma microenvironment[22]. In ovariectomised (OVX) mice, FOXF1 was expressed in bone marrow-derived macrophages (BMMs)[23]. Therefore, FOXF1 expression had a significant impact on the regulation of immune infiltration levels and tumor-immune interaction in ovarian cancer. Gene copy number alterations are common in cancer and are closely associated with recurrence and death of cancer. Amplification, deletion and mutation are common ways in which genes change[24]. Our results showed most genetic variations in FOXF1 were deep deletion. The deep deletion of FOXF1 was also associated with immune cell infiltration of B cells, CD8 + T cells and Tregs. Therefore, deep deletion of FOXF1 may also be associated with immune cell infiltration in ovarian cancer.

In order to explore biological function and signaling pathways which were related to FOXF1 in ovarian cancer, the genes co-expressed with FOXF1 has been identified. After that, functional enrichment analyses showed FOXF1 mainly involved in cell adhesion, NADH dehydrogenase complex, MHC protein complex, cytokine binding and rRNA binding. KEGG pathway analysis denoted that FOXF1 was mainly enriched in the pathways involved in DNA replication and ECM-receptor interaction. Overexpression of FOXF1 correlated with decreased expression of vascular cell adhesion molecule-1 (VCAM-1) in mice[25]. The expression of some cytokine factors could also be regulated by FOXF1[26]. In addition, depletion of FOXF1 in breast cancer cells led to increased DNA replication[27]. These results suggest that FOXF1 affects the malignant progression of ovarian cancer through a variety of modulatory mechanisms.

To further study the molecular mechanism of FOXF1 in ovarian cancer, kinase, miRNA or transcription factor targets which were related to FOXF1 have also been shown in the present research. PRKG1, miR-151 and SRF have been regarded as hub targets of FOXF1 in the study. These hub targets mainly participated in the regulation of calcium ion transport, cell division, homotypic cell-cell adhesion and pri-miRNA transcription by RNA polymerase II. PRKG1 has been reported as a diagnosis and prognostic factor in ovarian cancer[28, 29]. In ovarian cancer, miR-151 could also inhibit proliferation and migration of cancer cell through regulate MEX3C level[30]. As a transcription factor, SRF has been shown to regulate cell proliferation and motility of ovarian cancer[31]. Therefore, our analyses suggest that PRKG1, miR-151 and SRF are key targets of FOXF1. FOXF1 is likely to affect the development of ovarian cancer through regulate the expression of these genes.

Besides, we used CMap to screen out several potential small molecules for ovarian cancer treatment, like veliparib, PD-0325901 and prazosin. Veliparib with first-line chemotherapy could enhance progression-free survival rate in ovarian cancer patients[32]. Veliparib with carboplatin and paclitaxel could also improve progression-free survival rate in patients with germline BRCA mutation-associated advanced breast cancer[33]. MEK inhibitor PD-0325901 may also be used in advanced ovarian cancer[34]. Prazosin, a non-selective α1-adrenoceptor and a selective α2B-adrenoceptor antagonist, is reported to possess anti-cancer activity in some types of cancer[35, 36]. However, the therapeutic potential of prazosin in ovarian cancer has not been studied. In conclusion, the small molecular compounds screened in this study, such as veliparib, PD-0325901 and prazosin, may play important roles in inhibiting the progression of ovarian cancer.

Conclusions

In summary, our study performed integrated analyses for the significance of FOXF1 in diagnosis of ovarian and its potential role in tumor-immune interaction. Key targets and signal pathways of FOXF1 in ovarian cancer were first proved. In the end, several potential small-molecules for ovarian cancer treatment have also been found through analyzed FOXF1 related DEGs. However, these results are subject to certain limitations. The functional mechanisms of FOXF1 still require further experimental validations, owing to differences found among databases, limited sample sizes, and few relevant experimental studies.

Materials And Methods

Analysis of FOXF1 Expression in Various Cancers and ovarian cancer

The mRNA expression levels of FOXF1 in various cancers and their normal tissue counterparts were analyzed using the Oncomine database (<https://www.oncomine.org/resource/login.html>), GEPIA (<http://gepia.cancer-pku.cn/>) and TIMER (<http://cistrome.dfci.harvard.edu/TIMER/>). In GEPIA, the expression data of FOXF1 in tumor samples and adjacent samples included the data in The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx). FOXF1 mRNA expression in ovarian cancer and normal tissue was examined in the Oncomine database and the Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>). The difference associated with $p < 1E-4$ and $|log fold change (FC)| > 2$ was considered significant in Oncomine. The dataset of accession numbers GSE66957 was downloaded from the GEO database. The database including 12 normal samples and 57 tumor samples. These data were standardized by R package "limma". Expression differences of FOXF1 were analyzed by t-test. Gene expression profile matrix files of ovarian cancer samples and normal Ovarian tissue samples were from TCGA database and GTEx database separately.

Association between FOXF1 Expression and Clinical Characteristics of ovarian cancer

The expression level of FOXF1 in assorting subgroups were dissected by using UALCAN website (<http://ualcan.path.uab.edu/>). UALCAN is an effective website for online data analysis and digging based on TCGA, such as biomarker identification, and analyses of gene expressions, DNA methylation and survival. FOXF1 mRNA expression in cancer was separately analyzed with patient characteristics of sample types, individual cancer stage, age, race, gender, TP53 mutant and tumor grade compared to the normal tissue expression. The statistical analysis between two variables was performed by unpaired t-test.

Correlation between FOXF1 expression and CNV and immune cell infiltration

TIMER2.0 (<http://timer.cistrome.org/>) was used to unearth the correlation between FOXF1 expression and infiltration level of different immune cells. CBioPortal(<https://www.cbioportal.org/>) was used to analyze CNV of FOXF1 in ovarian cancer. TIMER2.0 was used to compare immune infiltration distribution by the CNV status of FOXF1 in ovarian cancer. TIMER2.0 website is used for comprehensive analysis of tumor infiltrating immune cells (TIIC) and provides 6 analysis modules such as the correlation between TIIC abundance and gene expression, overall survival, somatic mutation, and DNA somatic CNV, differential gene expression and gene correlation analysis[17]. TIMER2.0 web server offers immune infiltration algorithms like TIMER, CIBERSORT, quanTlseq, xCell, MCP-counter and EPIC.

Profiling of Genes Co-Expressed and enrichment analysis with FOXF1

LinkedOmics website (<http://www.linkedomics.org/login.php>) was employed to investigate co-expression genes of FOXF1 in TCGA-OV dataset. Pearson correlation coefficient was used for statistical analysis. Significance was analyzed by bilateral test. Genes with false discovery rate (FDR) less than 0.01 were taken as co-expressed genes of FOXF1. To analyze co-expressed gene functional network, GSEA was used to unravel co-expressed genes of FOXF1 for GO functional annotation (biological process, cellular component, molecular function), KEGG pathway analysis and enrichment analysis of targets of kinases, miRNAs and TFs based on MSigDB. Test times were set at 1000. Pathways with threshold value FDR less than 0.05 were chosen as enriched pathways.

Target networks of kinases, miRNAs and transcription factors (TFs) of FOXF1 in ovarian cancer

GeneMANIA (<http://genemania.org/>) website was used to build protein protein interaction (PPI) network using kinase, miRNA and TF with the smallest FDR value. GeneMANIA website can be utilized to generate speculation of relevant gene functions, analyze gene lists, and determine gene priority through functional analysis. Genes with similar functions can be searched in a gene list combining genomics and proteomics data. The second function of GeneMANIA is gene function prediction. By giving a searching gene, GeneMANIA can discover genes with shared functions according to interaction.

CMap predicts underlying drugs of ovarian cancer associated with FOXF1

First, tumor samples and normal samples were analyzed ($|logFC| > 2.0$, $FDR < 0.05$) to recognize DEGs associated with ovarian cancer. Upregulated and downregulated DEGs related to ovarian cancer were overlapped with co-expressed genes significantly correlated with FOXF1. DEGs co-expressed with FOXF1 in ovarian cancer were obtained. The above genes were input to Connectivity Map database (<https://clue.io/query>) to screen potential small molecules in ovarian cancer. Gene set enrichment analysis was used to obtain small molecules with value from -1 to 1. Small molecules with negative values present it has the potential to reverse the state of ovarian cancer cells.

Abbreviations

miRNAs: microRNAs; TFs: transcription factors; CMap: Connectivity Map; CRC: colorectal cancer; NSCLC: Non-Small-Cell lung cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; GEPIA: Gene expression Profiling Interactive Analysis; Tregs: T cell regulatory; CNV: copy number variation; GSEA: gene set enrichment analysis; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; BPs: biological process; CC: Cellular component; MF: Molecular function; DEGs: differentially expressed genes; PTC: papillary thyroid cancer; MCP-1: monocyte chemoattractant protein 1; OVX: ovariectomized; BMMs: bone marrow-derived macrophages; VCAM-1: vascular cell adhesion molecule-1; GTEx: Genotype-Tissue Expression; GEO: Gene Expression Omnibus; FC: fold change; TIIC: tumor infiltrating immune cells; FDR: false discovery rate; PPI: protein protein interaction.

Declarations

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None.

Author' contributions

Xiang Zhang and Jiping Liu designed and performed this study. Jinghong Chen and Fangfang Wang assisted in carrying out the research. Meng Zhang assisted in editing language. Xiang Zhang and Fangfang Wang assisted in analyzing the data. Jiping Liu proofread the manuscript. All authors have approved the final manuscript. Therefore, all authors have full access to all the data in the study and take responsibility for the integrity and security of the data.

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Availability of data and materials

All data generated or analyzed during this study could be obtained upon reasonable request to the corresponding author.

Ethics approval and consent to participate

None.

Consent for publication

All authors have given consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

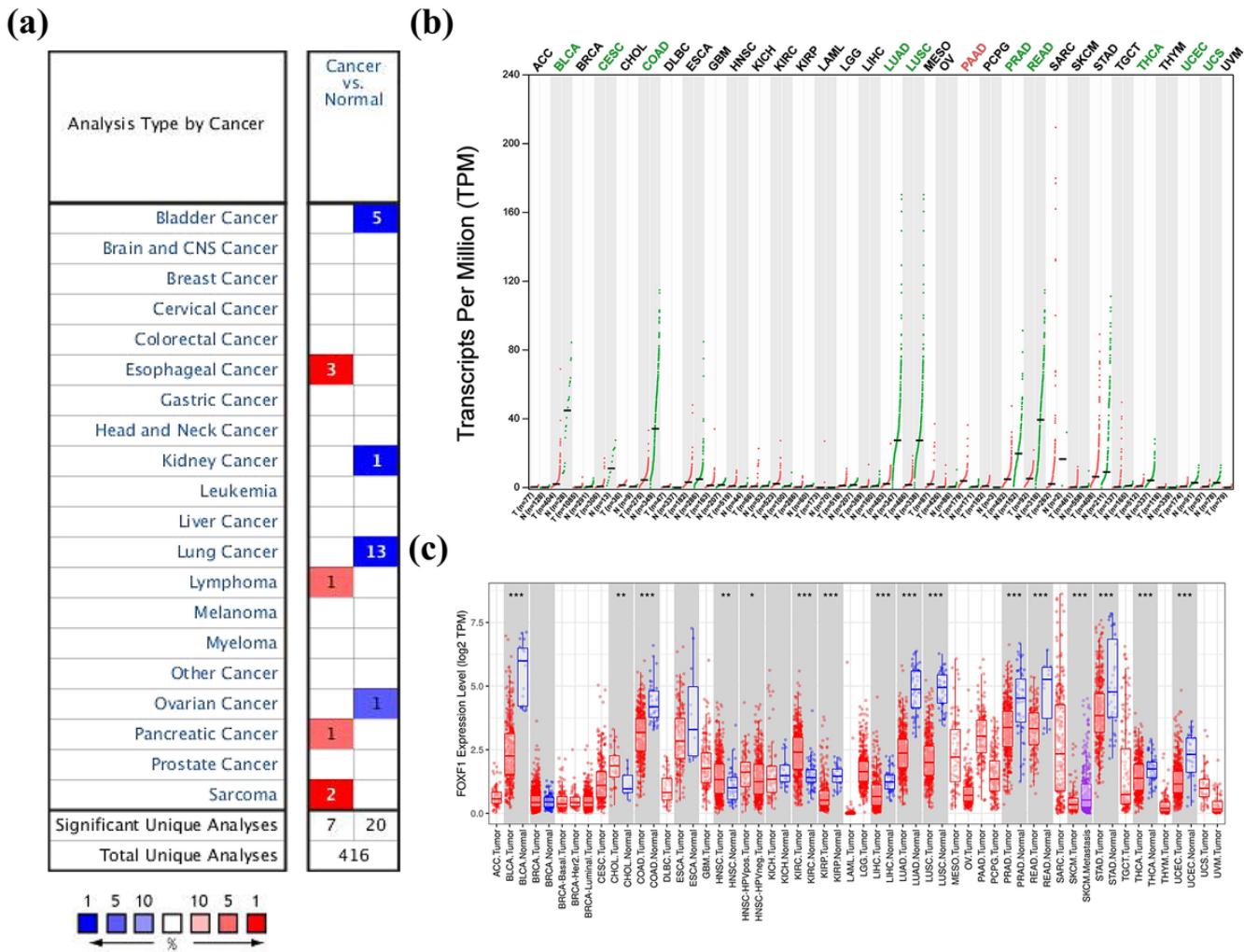


Figure 1

The expression of FOXF1 in various cancers a Oncomine database analysis results: compared with normal tissues, the number of data sets with higher expression of FOXF1 mRNA (left column, red) and lower expression of FOXF1 mRNA (right column, blue) in tumor tissues. b Expression analysis results of FOXF1 in 33 human cancers on GEPIA website: the red represents tumor samples, and the green represents normal samples. c TIMER database analysis results of FOXF1 expression: red boxes represent tumor tissues and blue boxes represent normal tissues (**p < 0.01, ***p < 0.001).

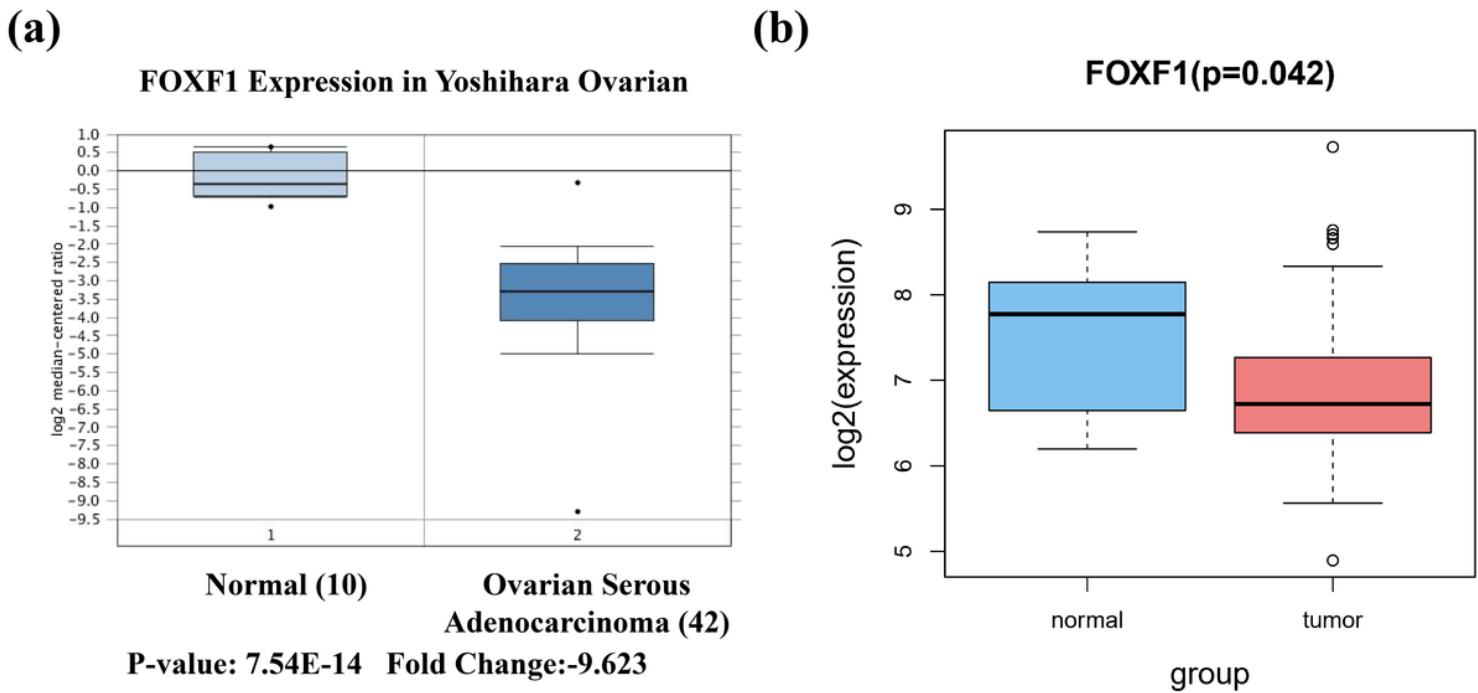


Figure 2

FOXF1 expression is markedly down-regulated in ovarian cancer a Box plot of FOXF1 expression in tumor tissue and normal tissue obtained from the Oncomine website analysis. b Box plot of FOXF1 mRNA expression in tumor tissue (red) and normal tissue (blue) obtained from GEO database.

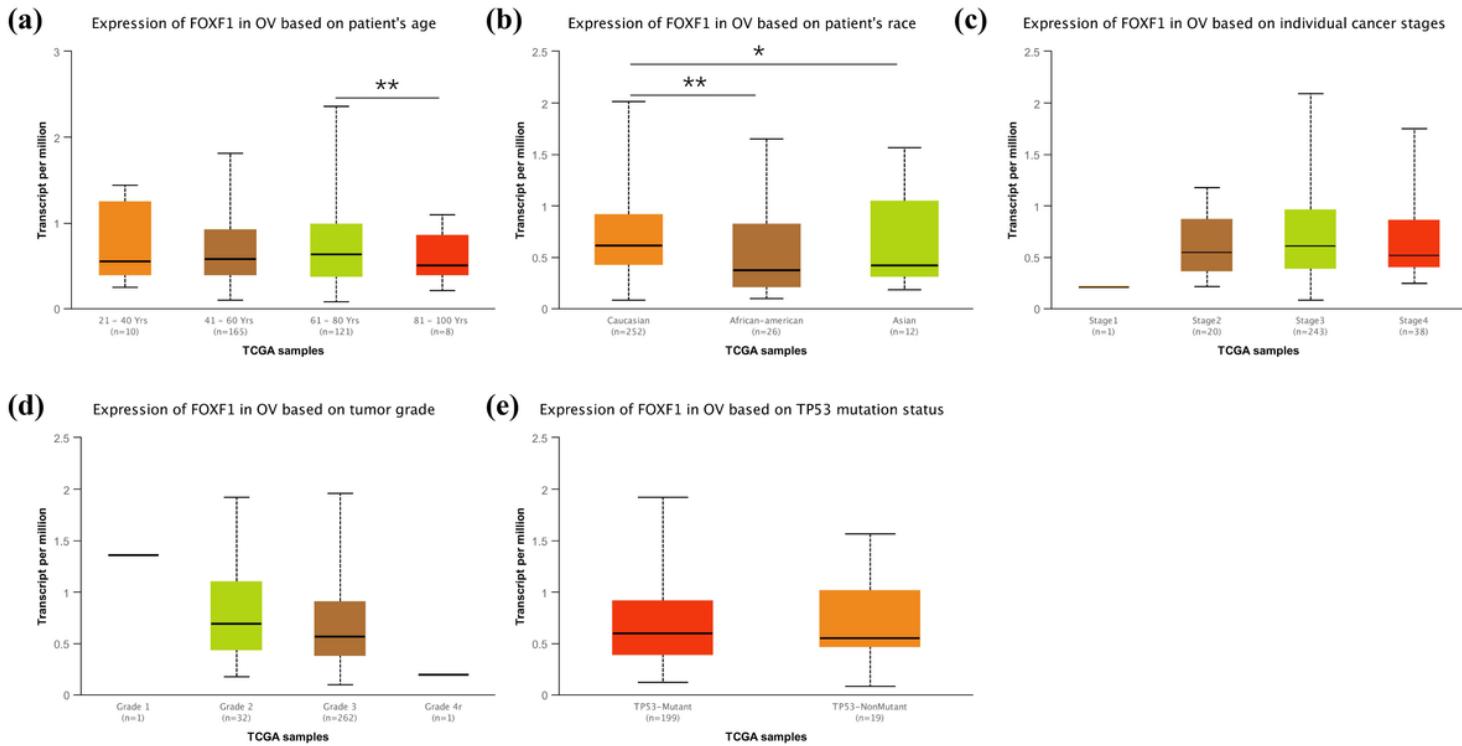


Figure 3

Correlation between FOXF1 expression and clinical features of ovarian cancer Through UALCAN database, box plots were drawn to illustrate the expression of FOXF1 mRNA in patients with different clinical features: (a) age, (b) race, (c) individual cancer stage, (d) grade, (e) TP53 mutation.

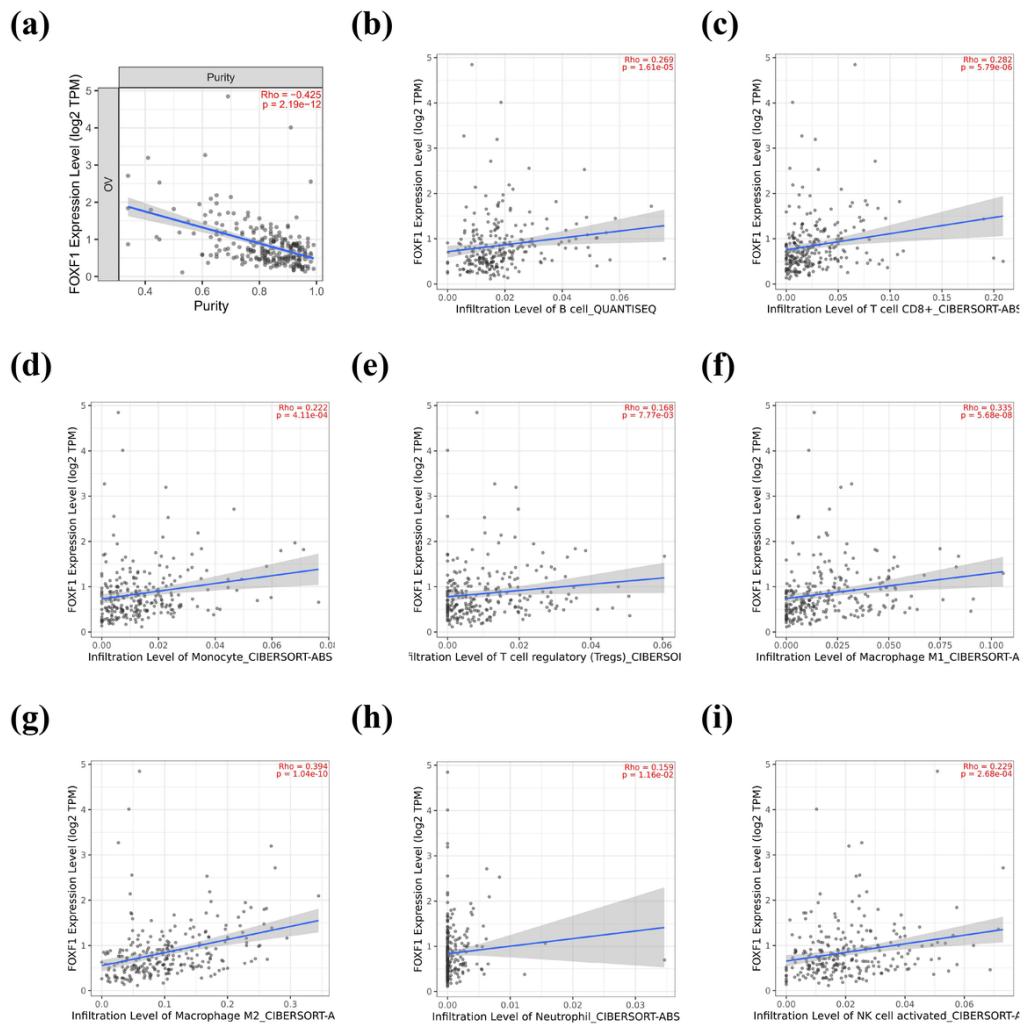


Figure 4

The correlation between FOXF1 expression and infiltration level of immune cells. The correlation between FOXF1 expression and tumor purity (a), B cells (b), CD8+ T cells (c), monocyte cells (d), Tregs (e), macrophage M1 (f), macrophage M2 (g), neutrophils (h), and NK cells (i).

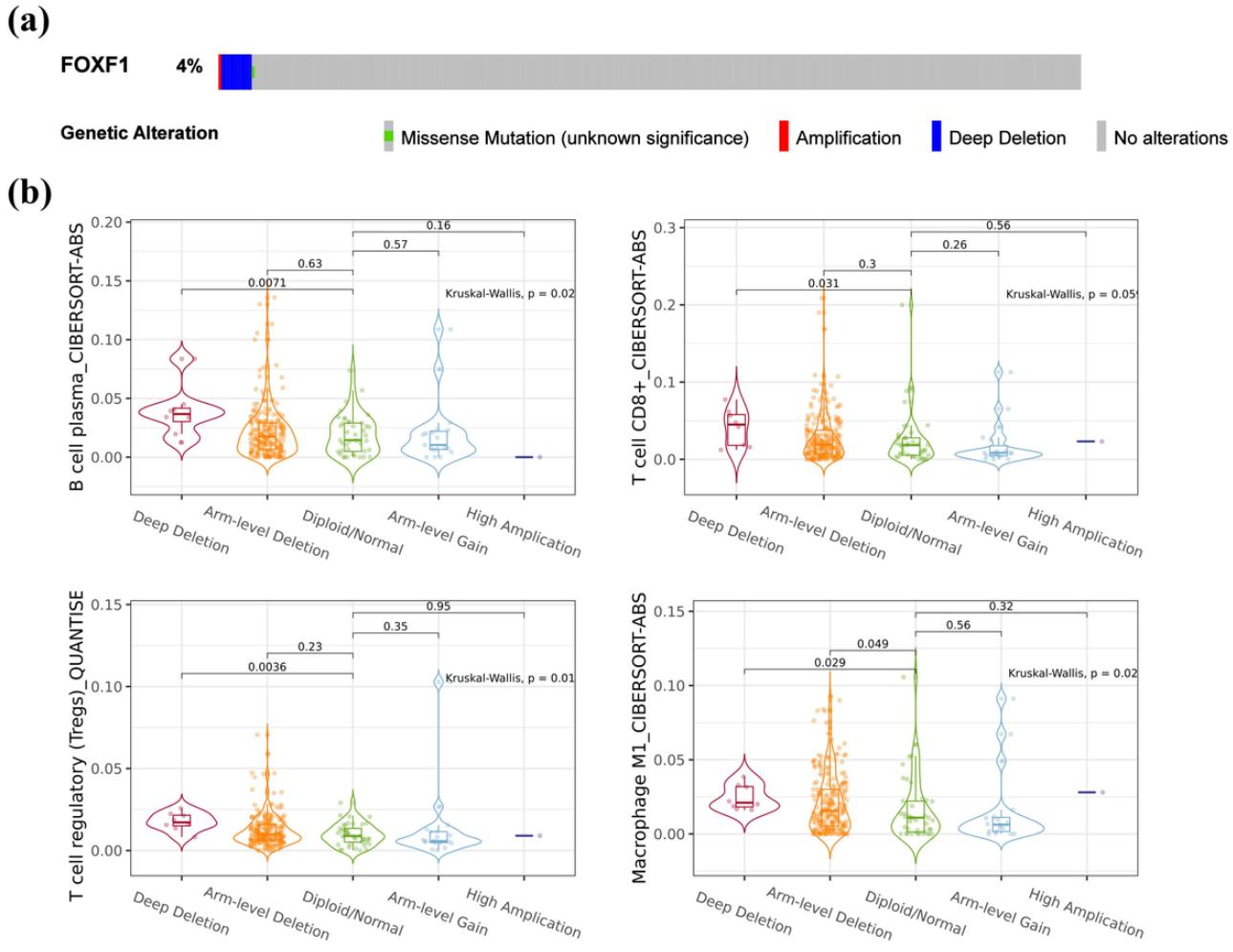


Figure 5

Correlation analysis between CNV of FOXF1 and immune infiltrates a Analysis of genetic variations in FOXF1. b The CNV level of FOXF1 in different immune cells.

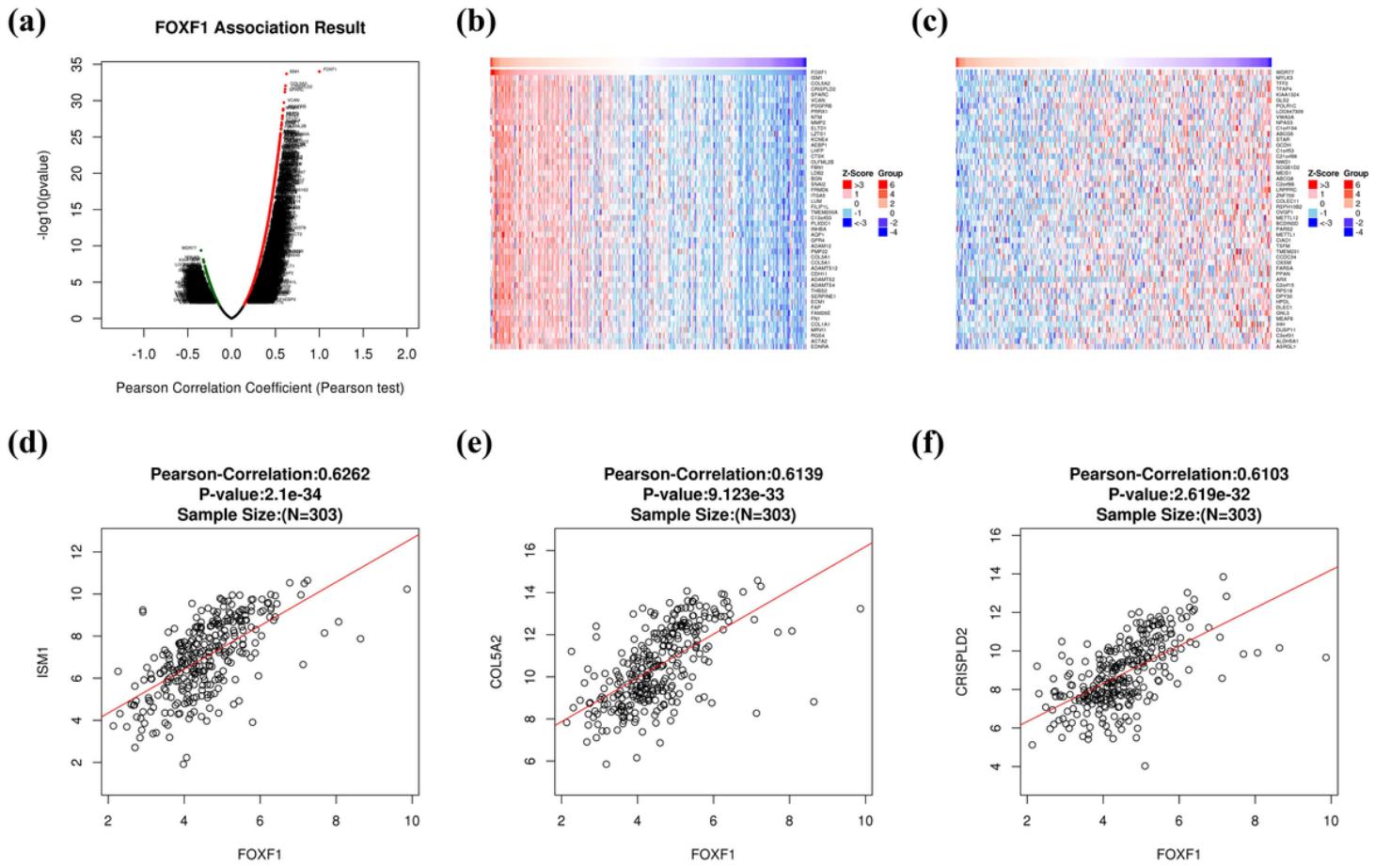


Figure 6

Genes in correlation with FOXF1 in ovarian cancer a The Pearson test was employed to analyze the genes related to FOXF1 expression in ovarian cancer. The red dots represent genes with a prominent positive correlation, the green dots represent genes with a notable negative correlation, and the black represents no significant correlation. (b, c) Heat maps present the genes (top 50 each) positively correlated and negatively correlated with ovarian cancer. (d, e, f) Scatter plots clarify the Pearson correlation between FOXF1 expression and ISM1 (d), SLCO2A1 (e) and TEK (f) expression.

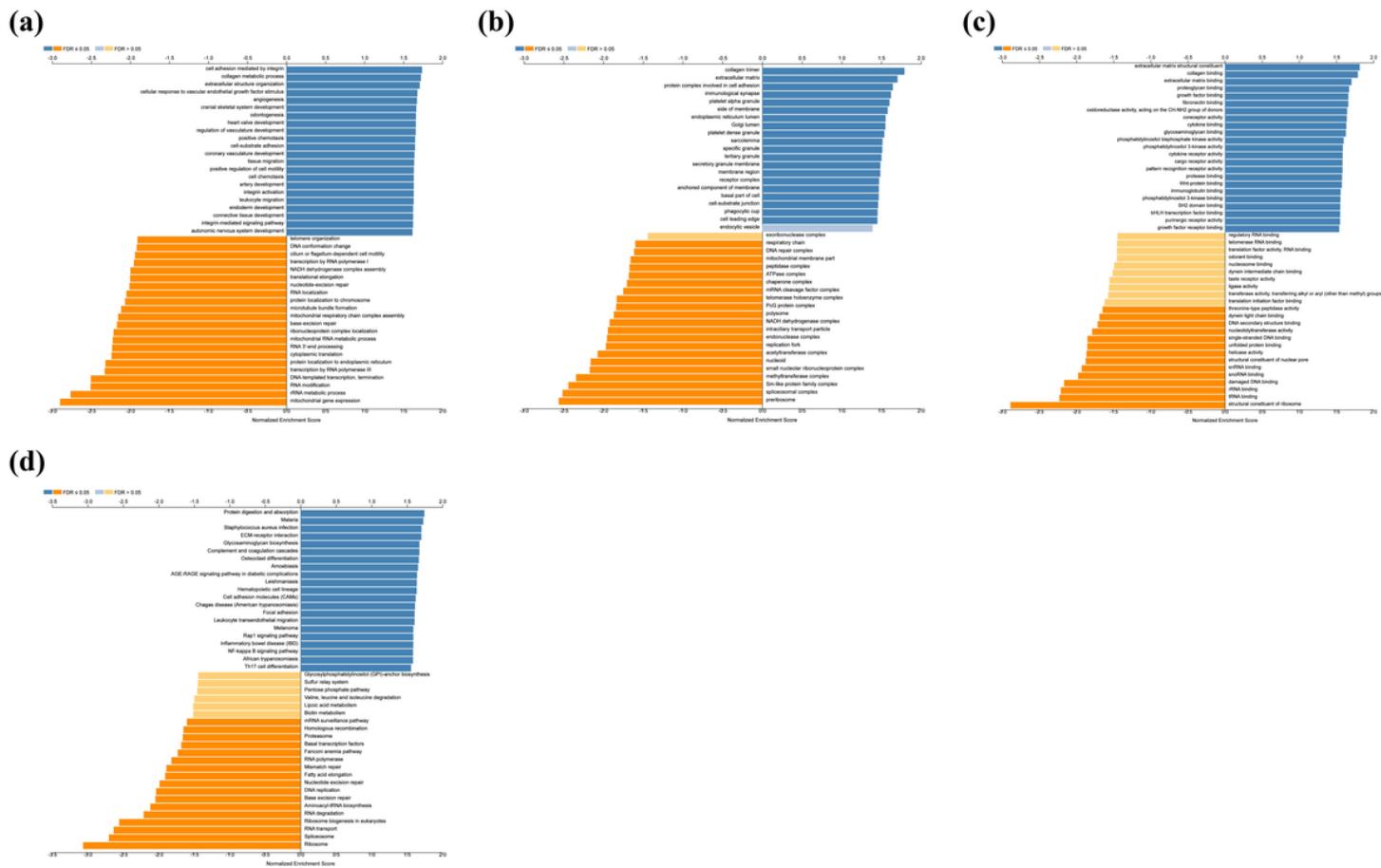


Figure 7

Significantly enriched GO terms and KEGG pathways in ovarian cancer a Biological process (BP). b Cellular component (CC). c Molecular function (MF). d The results of KEGG pathway analysis.

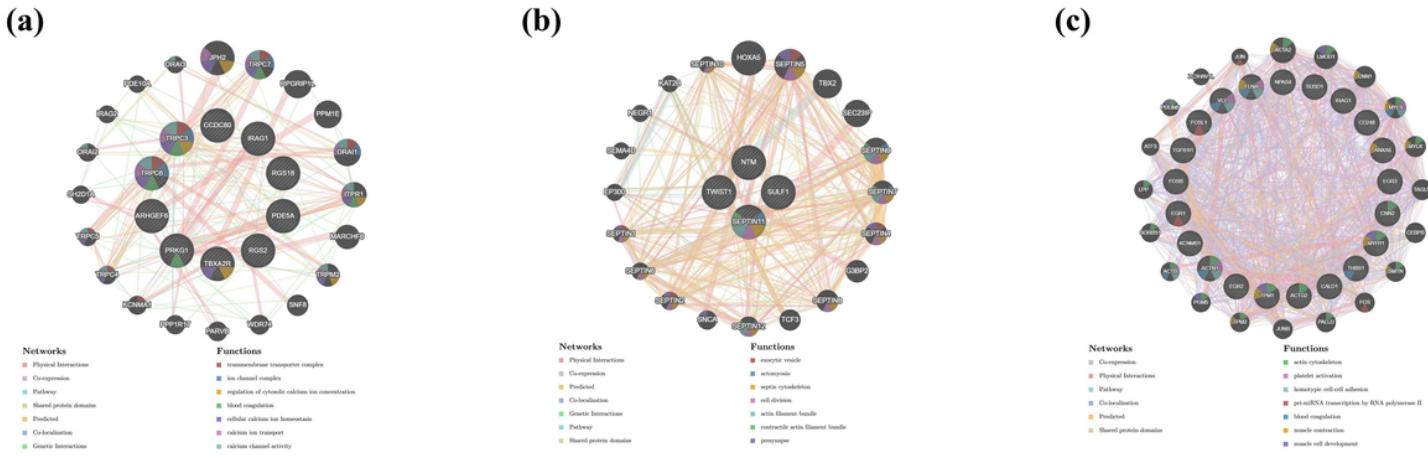


Figure 8

networks and functional analysis networks of (a) kinase PRKG1. (b) miR-151. (c) Transcription factor SRF. Different colors of the network edge indicate the bioinformatics methods applied: co-expression, website prediction, pathway, physical interactions and co-localization. The different colors for the network nodes indicate the biological functions of genes.

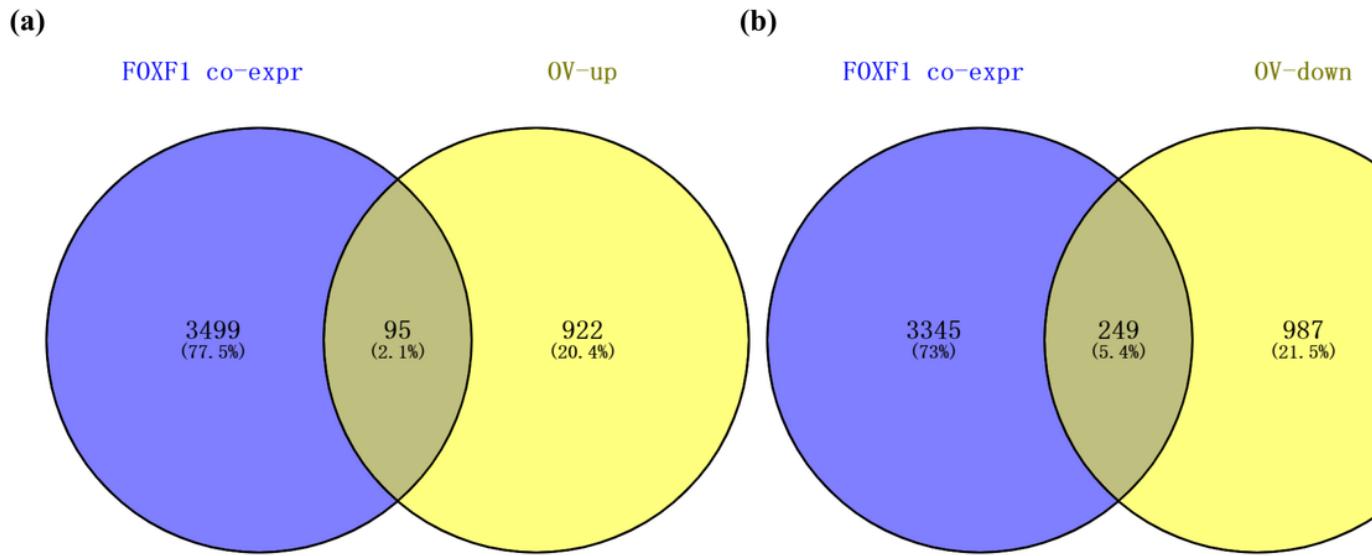


Figure 9

Analysis of FOXF1 related DEGs a Venny diagram of co-expressed genes of FOXF1 and upregulated DEGs. b Venny diagram of co-expressed genes of FOXF1 and downregulated DEGs.