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Comprehensive in silico analysis of prognostic and immune infiltrates for FGFs in human ovarian cancer

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Abstract

Background Fibroblast growth factors (FGFs) are cell signaling proteins that perform multiple biological processes in many biological processes (cell development, repair, and metabolism). The dynamics of tumor cells, such as angiogenesis, transformation, and proliferation, have a significant impact on neoplasia and are modulated by FGFs. FGFs' expression and prognostic significance in ovarian cancer (OC), however, remain unclear.

Methods Through a series of in silico analysis, we investigated the transcriptional, survival data, genetic variation, gene-gene interaction network, ferroptosis-related genes, and DNA methylation of FGFs in OC patients.

Results We discovered that while FGF18 expression levels were higher in OC tissues than in normal OC tissues, FGF2/7/10/17/22 expression levels were lower in the former, and that FGF1/19 expression was related to the tumor stage in OC patients. According to the survival analysis, the clinical prognosis of individuals with OC was associated with the aberrant expression of FGFs. The function of FGFs and their neighboring genes was mainly connected to the cellular response to FGF stimulus. There was a negative correlation between FGF expression and various immune cell infiltration.

Conclusions This study clarifies the relationship between FGFs and OC, which might provide new insights into the choice of prognostic biomarkers of OC patients.

Keywords Ovarian cancer, Fibroblast growth factors, Prognostic value, Bioinformatics analysis, Tumor microenvironment

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Introduction

Ovarian cancer (OC) is the leading cause of gynaecological oncology-related deaths worldwide, with over 300,000 new cases of OC diagnosed and 18,000 patients dying from their disease each year [1]. Due to late diagnosis, quick disease development, recurrence, and treatment resistance, OC mortality is high. 75% of patients are diagnosed with stage III or IV, and 75% of these patients die within 5 years [2]. In contrast, long-term survival (>10 years) was 80–95% in patients with stage I or II [2]. OC includes three main types: epithelial, stromal, and germ cell cancers, of which epithelial OC is the most common type (almost 90%) [3]. Thus, efficient early diagnostic/prognostic indicators for OC are urgently needed.

A family of cell signaling proteins known as fibroblast growth factors (FGFs) perform a wide variety of biological tasks [4, 5]. A total of 18 FGFs have been identified since the 1970s, when FGF1 and FGF2 were first identified [6]. Formerly known as FGF11–FGF14, although they share a great deal of sequence similarity with the FGF family, but do not activate the FGF receptor (FGFR), are not typically regarded as FGF family members [6, 7]. FGFs can be categorized into 6 categories (FGF1/2, FGF3/7/10/22, FGF4/5/6, FGF8/17/18, FGF9/16/20, and FGF19/21/23) based on sequence homology and phylogenetic differences [6]. FGFs play a significant role in controlling the autocrine and paracrine actions of stromal and neoplastic cells. Therefore, they might be crucial in several biological processes like the development of tumors and treatment resistance [8]. Human malignant tumors including OC [9], cervical cancer [10], gastric cancer [11, 12], breast cancer [13], liver cancer [14], lung cancer [15], colorectal cancer [16], and acute leukemia [17] all exhibit aberrant expression of FGFs.

FGFs interact with FGFRs, which are made up of four transmembrane receptors: FGFR1-4, to initiate signaling [7]. A FGFR consists of a single-pass transmembrane domain, a cytoplasmic tyrosine-kinase domain, and three extracellular immunoglobulin-like domains (D1–D3) [7]. The presence of an acidic, serine-rich segment known as the "acid box" in the linker between D1 and D2 is a distinguishing feature of FGFRs. The D1 domain and the acid box are thought to have a role in receptor autoinhibition, whereas the D2-D3 portion of the FGFR ectodomain is essential and sufficient for ligand binding and specificity [6]. The D1 domain and/or acid box are removed from FGFR1-FGFR3 to create FGFR1-3, also known as IIIb and IIIc. FGFR IIIb is expressed by epithelial cells while FGFR IIIc is often expressed by mesenchymal cells. Since the FGFR4 gene is not subject to alternative splicing, it lacks isoforms [18].

Numerous cancer types, skeletal system anomalies, developmental disorders, chondrodysplasia, corneal neovascularization, and X-linked hypophosphatemic rickets are among the diseases that are influenced by dysregulated FGF signaling [19]. In addition, some evidence suggests that mutations in the somatic FGFR gene or overexpression of ligands or receptors can lead to various malignancies due to abnormal FGF activity [20, 21]. Increased expression of FGF3 DNA amplification was observed in OC in a study by Rosen A et al. [9], and further research raised the possibility that elevated FGF3 expression might be linked to a malignant phenotype [1]. Lingling Hu et al. [22] found that the FGF19-FGFR4 signaling pathway can encourage the spread and invasion of OC through the AKT-MAPK signaling pathway. In patients with OC indicative of advanced illness, Teben PJ et al. [23] discovered higher FGF23 concentrations. By suppressing FGFR2 and FGFR1, Claire Cole et al. [1] showed that cisplatin sensitivity in OC can be enhanced.

However, various FGFs have different biological activities in OC, and their expression levels, genetic variation, molecular mechanisms, prognostic value, and relationships with prognosis and immunological infiltration in OC patients have not yet been thoroughly explained. Using multiple large-scale bioinformatics databases, an extensive and thorough bioinformatic investigation of the expression of FGFs in OC was carried out in this study.

Materials and methods

Transcriptomic analysis

The Cancer Genome Atlas (TCGA) RNA-Seq expression data was used to assess tumor samples and normal samples by Gene Expression Profiling Interactive Analysis (GEPIA, www.gepia.cancer-pku.cn). Differential expression analysis, cancer type staging, cancer pathology staging, correlation analysis, related gene detection, and dimensionality reduction analysis are the functions that GEPIA can provide [24].

Proteomics analysis

Transcriptomics, antibody-based immunofluorescence microscopy, and mass spectrometry validation were combined to create the Human Protein Atlas (HPA, www.proteinatlas.org) [25]. We used it to compare the expression of FGFs in OC tissues and normal tissues.

DNA methylation analysis

MEXPRESS (https://mexpress.be/) integrates and displays clinical data from TCGA as well as data on DNA methylation [26]. We examined the pathways of dysregulated DNA methylation in FGFs using MEXPRESS.

Survival analysis

The Kaplan-Meier Plotter (www.kmplot.com) is a database of survival data for clinical cancer patients [27]. We

used it to examine OS and RFS in OC patients. *P*-values lower than 0.05 were regarded as statistically significant.

Gene-gene interaction analysis

GeneMANIA (www.genemania.org) [28] can be used to query and generate a list of genes that are functionally comparable to target genes. We use it to create a network of gene-gene interactions for FGF in this study.

Protein-protein interaction analysis

All publicly accessible protein-protein interaction (PPI) data sources are gathered, scored, and integrated by STRINGS (www.string-db.org), which also adds computation and prediction to the mix [29]. To examine their interactions, we used STRINGS to conduct a PPI network analysis of FGFs.

Genetic variation analysis

The cBioPortal (www.cbioportal.org) provides analysis, and download of large-scale cancer genomics data sets [30]. Using cBioPortal, we further examined the expression of FGFs in the ovarian serous cystadenocarcinoma dataset from the TCGA database.

Enrichment Analysis

Metascape (https://metascape.or) is a bioinformatics database for enrichment analysis [31]. We performed functional annotation and pathway enrichment analyses of FGFs and neighboring genes that were significantly related to FGFs using Metascape. A database of biological pathway models can be found at WikiPathways (https://www.wikipathways.org) [32]. WikiPathways provides data on all the genes involved in the ferroptosis pathway.

Immune infiltrates analysis

TIMER (www.cistrome.shinyapps.io) was utilized to estimate the clinical significance of tumor-infiltrating immune cells and infer their abundance [33]. In this investigation, TIMER was employed to assess the relationship between the level of FGFs expression and immune cell infiltration as well as the relationship between the FGFs gene and genes related to ferroptosis (FRGs).

Pathway activity analysis

GSCA (http://bioinfo.life.hust.edu.cn/web/GSCA/) is a web server that conforms to multi-omics data based on the TCGA database [34]. The association between the FGFs gene pathway activity groups and FGFs gene expression profile data in OC was examined using GSCA.

Statistical analysis

Statistical analyses were conducted through R software (version 4.1.2). t-test was utilized to detect differences between groups. Differences in survival between high-expression and low-expression groups of OC patients were represented in Kaplan-Meier curves. Spearman and Pearson correlation analysis was conducted to calculate correlation coefficients. The threshold for statistical significance was set at $P<0.05$.

Results

Relationship between FGFs transcript levels and clinicopathological parameters in OC patients

We compared the levels of FGF transcripts in OC and normal samples using the GEPIA dataset (Fig. 1). Studies have revealed that OC tissue had lower levels of FGF2/7/10/17/20/22 transcription than normal ovarian tissue, and that OC tissue had higher levels of FGF1/3/8/18/19/21/23 expression than normal ovarian tissue. We also investigated the association between OC patient tumor stages and FGFs mRNA expression levels. The tumor stage was substantially correlated with the FGF1 and FGF19 groups ($P<0.05$), but not significantly different with the other groups (Fig. 2).

To further determine the protein expression of FGFs in OC, we used data from HPA to perform the analysis. We discovered that OC tissues exhibited significantly elevated levels of FGF2/7/9/10/17/19 proteins in comparison to the normal tissues (Fig. 3).

Relationship analysis between DNA methylation and expression of FGFs

We investigate the potential association between the DNA methylation of FGFs and the etiology of OC using the MEXPRESS (Fig. 4). We discovered that the expression of FGF1, FGF2, FGF3, FGF4, FGF18, FGF19, FGF20, and FGF21 was significantly positively correlated with the methylation levels of cg08816023, cg17214107, cg17277529, cg19831575, cg15699524, cg15774153, cg24030449, and cg13881341, respectively ($P<0.05$); and the expression of FGF7, FGF16, and FGF19 was significantly negatively correlated with the methylation levels of cg23504246, cg02096520, and cg26096837, respectively ($P<0.05$).

The prognostic value of FGFs in OC patients

We used Kaplan-Meier plotter analysis to determine the connection between FGFs at various transcription levels and clinical outcomes to assess the value of FGFs at various transcription levels in the progression of OC. The value of FGFs at various transcription levels in overall survival (OS) of OC patients was assessed (Fig. 5). According to the studies, prolonged OS was significantly linked with OC patients who had low mRNA expression of FGF1/7/9/18 and high mRNA expression of FGF5/8/16/20/21/22/23. Figure 6 depicts the recurrence-free survival (RFS) curve. Longer RFS

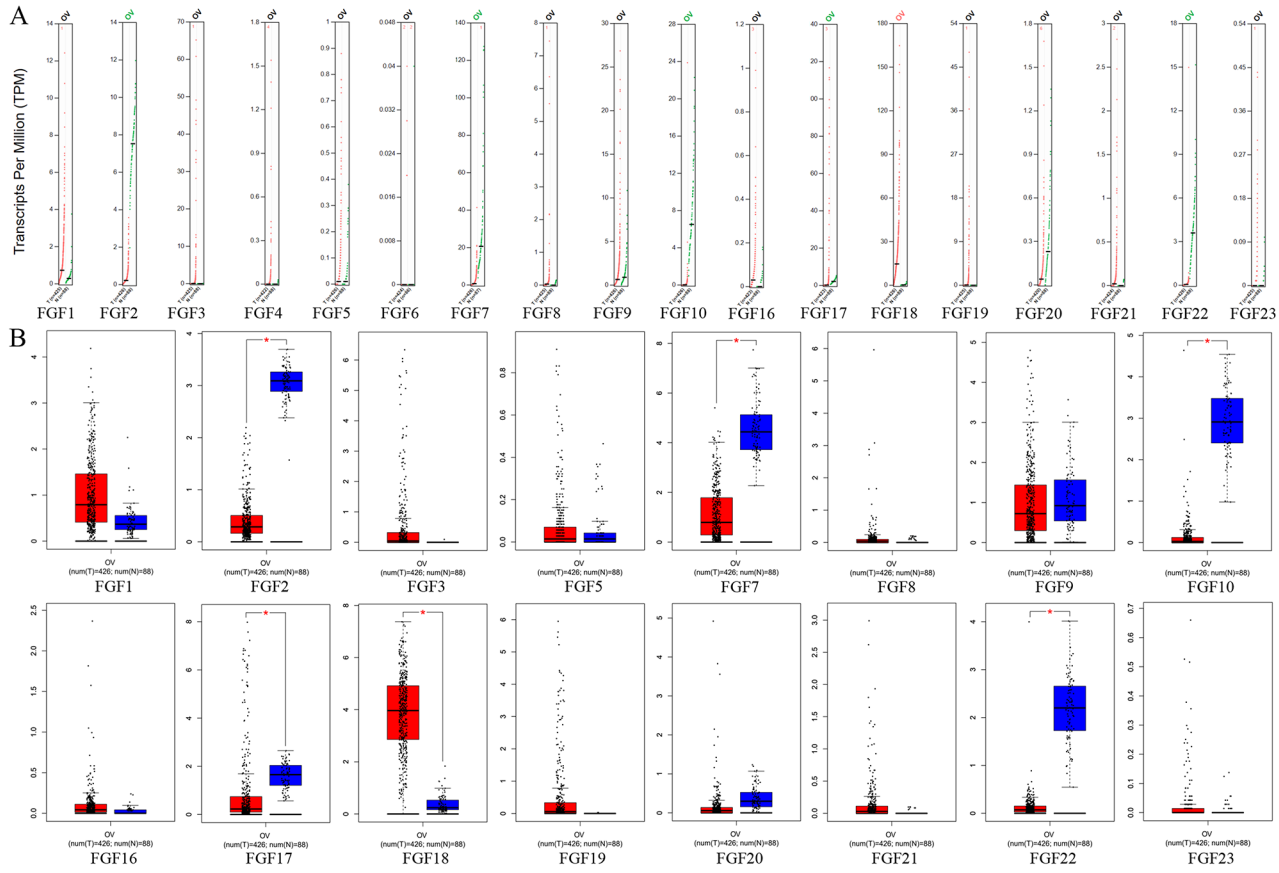


Fig. 1 The expression of FGFs in OC via GEPIA database. (**A**) scatter diagram. Red dots represent ovarian tumors and green dots represent normal tissue. (**B**) box plot. Red box plots represent ovarian tumors and blue dots represent normal tissue.The stars indicate statistical significance

was significantly linked with OC patients who had low transcription of FGF1/10/19 and high transcription of FGF3/6/8/16/17/21/23.

Genetic Alteration, co-expression, neighbor gene network, and interaction analyses of FGFs in OC patients

We examined genetic variation rate of FGFs in OC using the online application cBioPortal. 125 samples (40.19%) of the 311 OC patients exhibited altered FGFs (Figure S1A). The TCGA dataset shows that among FGFs, FGF23 had the highest genetic variation rate (11%) while FGF8 had the lowest mutation rate (0.8%). (Figure S1B). The co-expression connection between FGF6 and FGF23, FGF4 and FGF19, FGF3 and FGF4, FGF3 and FGF19, FGF17 and FGF20, FGF1 and FGF18 were significant($P<0.05$). FGF5 and FGF17, FGF5 and FGF22, FGF5 and FGF7 were mutually exclusive ($P<0.05$), according to the mutually exclusive evaluation of FGFs genes in the TCGA OC cohort (Figure S1C).

The GeneMANIA database was used to design a GGI network of FGFs and investigate those FGFs' functions (Figure S1D). There are 20 nodes surrounding the FGFs, which reflect genes that are connected to the FGFs through shared protein domains, physical interactions, co-localization, co-expression, prediction, genetic relationships, and pathways. These genes demonstrated the strongest connection with cellular responses to FGF stimulation, according to further functional analysis (FDR=9.47E-49). KL and FRS3 interact physically and pathway relationship with FGFs, with the exception of FGF21.

To investigate possible interactions between FGFs, we used STRING to conduct a PPI network analysis of the FGFs. FGFs proteins and 20 proteins that are very close to FGFs are present in the PPI network graph (Figure S2A). We performed functional annotation and pathway enrichment analysis on FGFs and the genes nearby using Metascape. Biological processes (6 entries), responseome gene sets (3 items), and wikipathway (3 things) made up the majority of the top 12 enrichments (Figure S2B, C, and Table 1). The occurrence and development of tumors were associated with a number of factors, including activating point mutations of FGFR2, the FGFR signaling pathway, FGFR2c ligand binding and activation, PI3K-Akt signaling pathway, FGFR2b ligand binding, and the

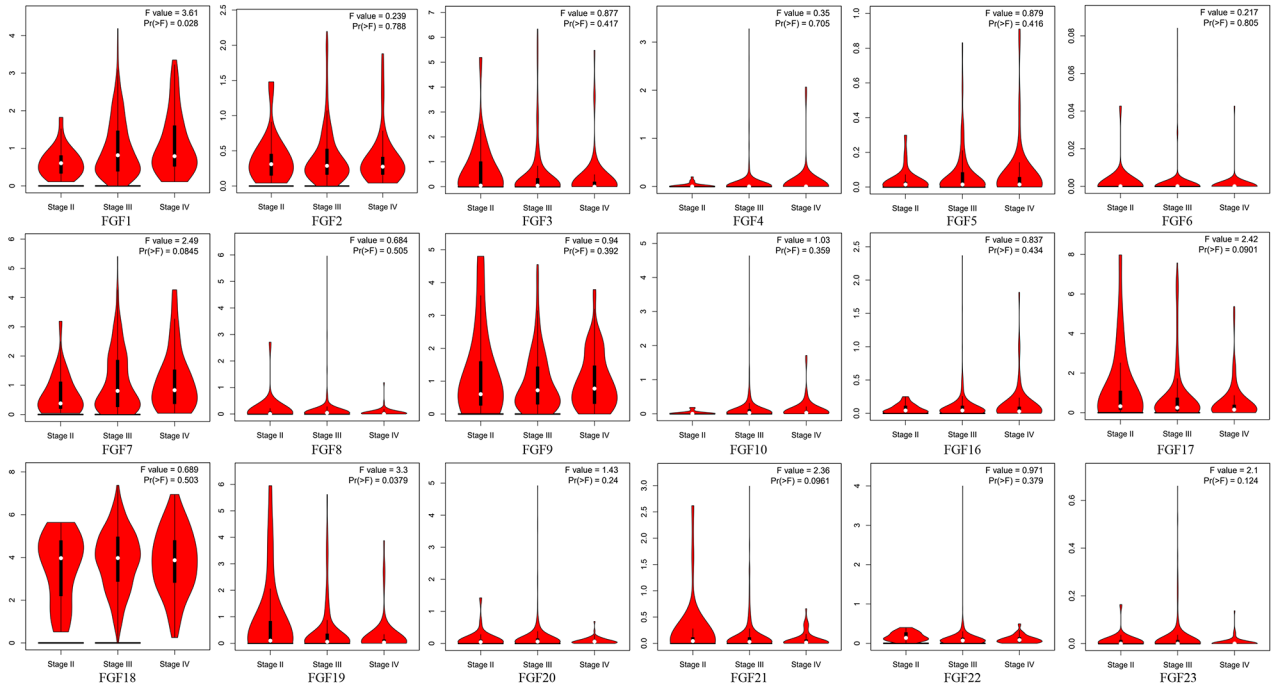


Fig. 2 Correlation between the expression of FGFs and tumor stage in OC via GEPIA database. Each subfigure represents the expression of FGFs in different Pathological Stage. Pr(> F): p-value of the F-test

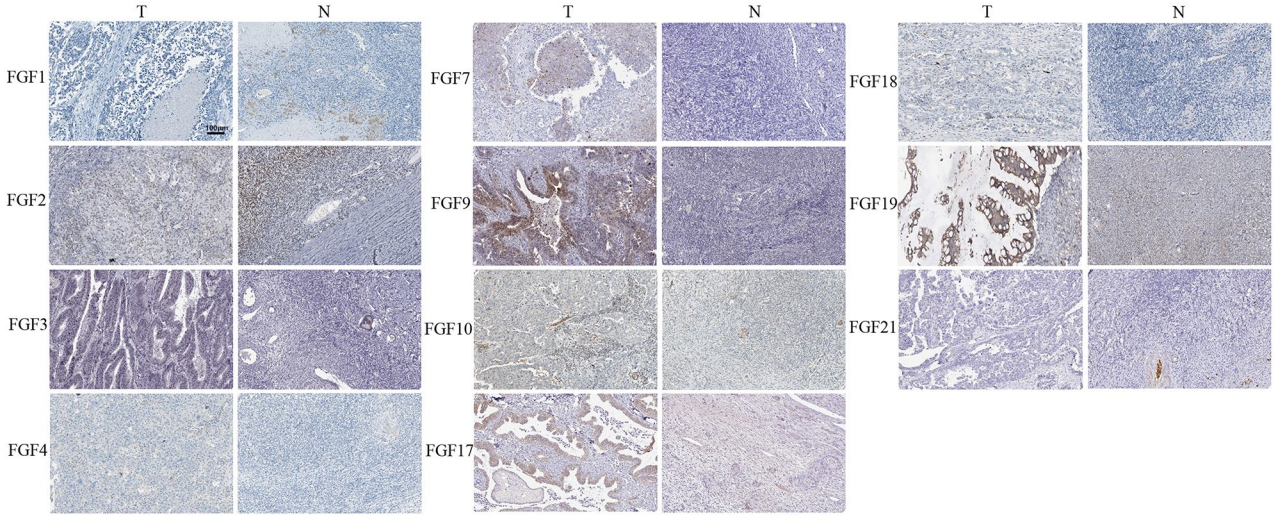


Fig. 3 Immunohistochemical analysis of FGFs expressions in OC samples. T: ovarian tumor tissue. N: normal tissue. Bar = 100 μm

positive regulation of ERK1 and ERK2 cascades, which were also involved in the tumorigenesis of OC.

Correlation analysis between FGF gene and FRGs

We used the cytoscape program to visualize the correlation analysis between the FGFs gene and the FRGs to investigate the underlying processes of the ferroptosis signals in OC. The co-expressed gene network (Figure S3A) revealed a relationship between GPX4, FTH1, and HMOX1 and FGF2/3/8/17/18/19/23. The gene most associated with *GPX4*, *FTH1*, and *HMOX1* was *FGF2* (Figure S3C).

The relationship between FGFs expression levels and Immune infiltration levels in OC

Using TIMER, the association between FGFs transcript levels and immune infiltration levels in OC was evaluated (Fig. 7). FGF2/7/20 expressions were negatively correlated with the infiltration of B cells (Fig. 7B, G, O). FGF3/4/21/22 expressions were negatively correlated

Fig. 4 Association between FGFs DNA methylation and the expression of (**A**) FGF1, (**B**) FGF2, (**C**) FGF3, (**D**) FGF4, (**E**) FGF5, (**F**) FGF6, (**G**) FGF7, (**H**) FGF8, (**I**) FGF9, (**J**) FGF10, (**K**) FGF16, (**L**) FGF17, (**M**) FGF18, (**N**) FGF19, (**O**) FGF20, (**P**) FGF21, (**Q**) FGF22, (**R**) FGF23. clinical stage simplified: stage1-pale yellow, stage2-flesh colored, stage3-pale purplish red, stage4-purplish red, null-pale gray. lymphatic invasion: purple-no, light blue-yes, null-pale gray. histological type: purple-serous cystadenocarcinoma, null-pale gray. new tumor event after initial treatment: purple-no, light blue-yes, null-pale gray. venous invasion: purple-no, light blue-yes, null-pale gray. sample type: purple-primary tumor, green-recurrent tumor, light blue-solid tissue normal(Refer to the legend with the illustration in the bottom right corner of Fig. 4)

with the infiltration of macrophage, neutrophil, and dendritic cells (Fig. 7C, D, P, Q), of which FGF3 expressions was also negatively correlated with the infiltration of CD8+ T cells. FGF5/6 expressions were negatively correlated with the infiltration of macrophage, of which FGF6 expressions was also positively correlated with the infiltration of CD4+ T cells(Fig. 7E, F). FGF8/9/17/18/19 expressions were negatively correlated with the infiltration of B cells, CD8+T cells, neutrophils, and dendritic cells, of which FGF8/17/18/19 expressions were also negatively correlated with the infiltration of macrophages (Fig. 7H, I, L, M, N).

Additionally, we use the TIMER to automatically output Cox regression findings and proofread B cells, CD8+T cells, CD4+T cells, macrophages, neutrophils, and FGF covariate factors. These investigations show a substantial correlation between the clinical outcomes of OC patients and the infiltration of CD4+T cells (P=0.010), neutrophils (P=0.038), and FGF23 (P=0.001). (Table 2).

Pathway activity analysis

Eight genes (FGF9/7/5/20/2/18/17/1) were significantly associated with OC signaling pathways, including apoptosis, cell cycle, DNA damage response, EMT, hormone AR, hormone ER, PI3K/AKT, RAS/MAPK, and RTK pathways, according to the related pathways network (Figure S4). FGF9, FGF7, FGF2, and FGF1 were mostly involved in the inhibition of apoptosis (21% inhibition vs. 4% activation), cell cycle (31% inhibition vs. 0% activation), cell cycle (37% inhibition vs. 0% activation), damage response (31% inhibition vs. 4% activation), respectively. However, the major activation pathways of FGF7 (38% activation vs. 3% inhibition), FGF5 (32% activation vs. 0% inhibition), FGF2 (41% activation vs. 3% inhibition), and FGF1 (25% activation vs. 3% inhibition) were all EMT.

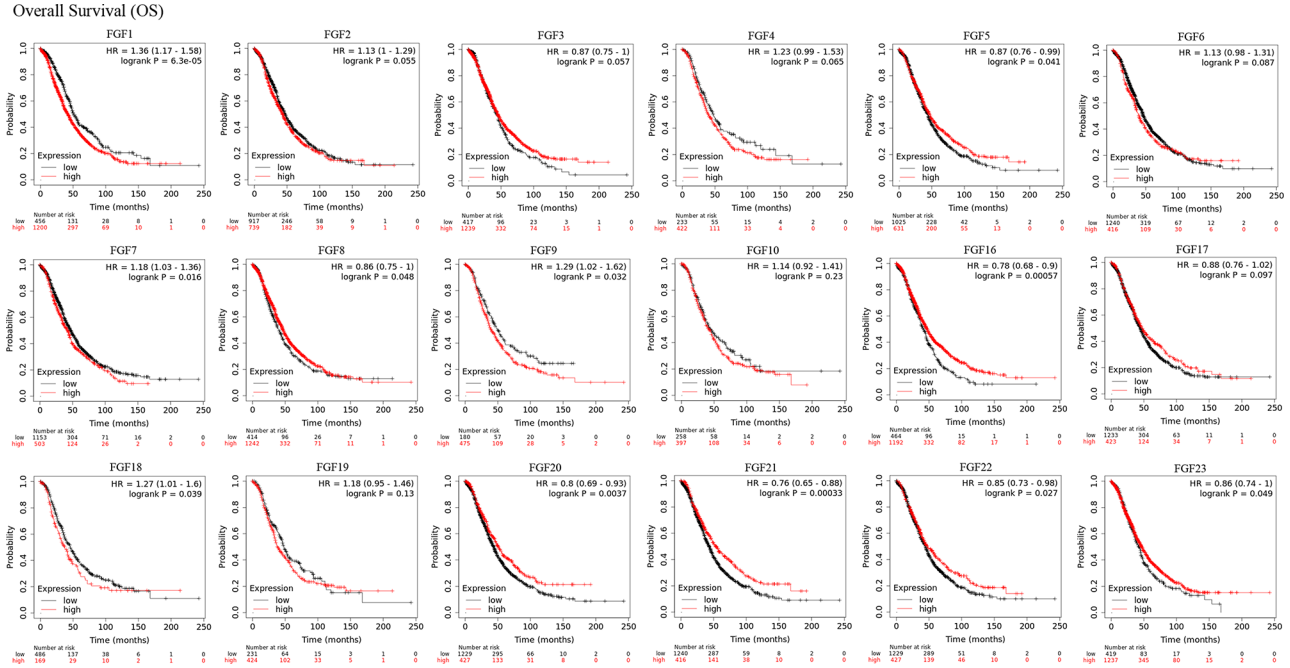


Fig. 5 Prognostic value of the transcript level of FGFs in OC patients in OS curves. Cutoff value separate the samples into two groups(high expression group and low expression group). OC: ovarian cancer. OS: overall survival. HR: hazard ratio. Survival time unit: months

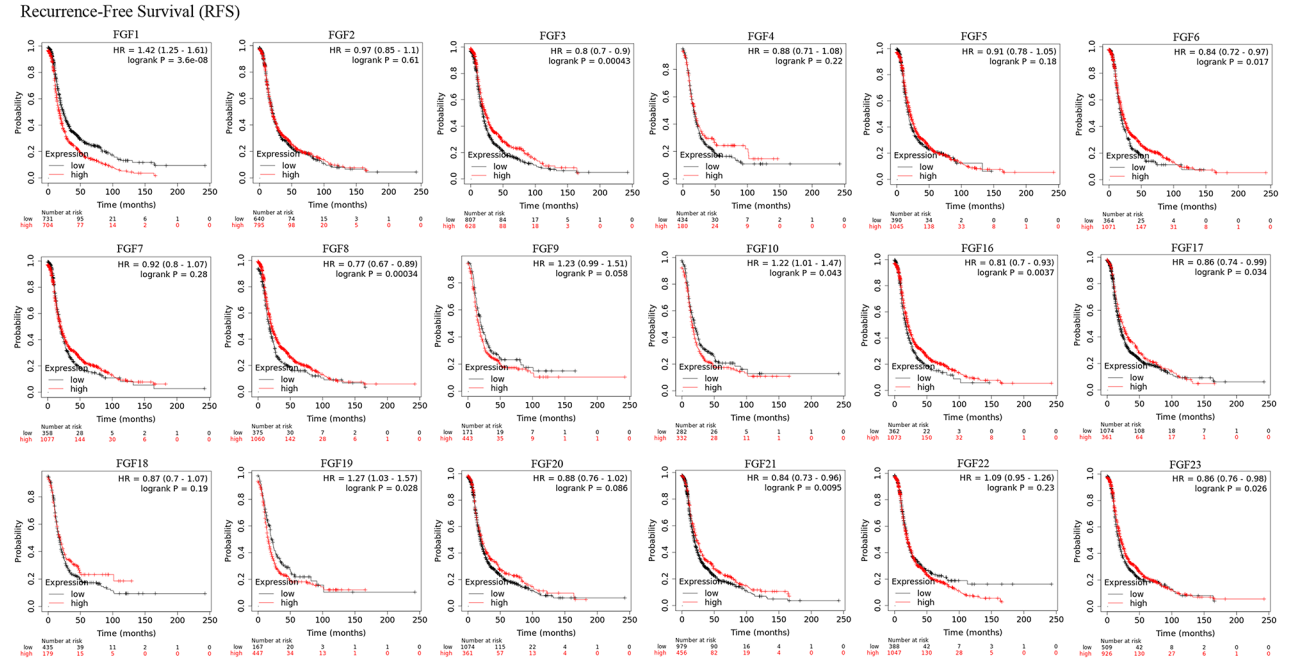


Fig. 6 Prognostic value of the transcript level of FGFs in OC patients in RFS curves. Cutoff value separate the samples into two groups(high expression group and low expression group). OC: ovarian cancer. RFS: recurrence-free survival. HR: hazard ratio. Survival time unit: months

Table 1 The function enrichment analysis of FGFs and neighbor genes in OV (Metascape)

GO	Category	Description	Count	%	Log10(*P*)	Log10(q)
R- HSA–2,033,519	Reactome Gene Sets	Activated point mutants of FGFR2	16	88.89	−54.94	−50.60
GO:0008543	GO Biological Processes	fibroblast growth factor receptor signaling pathway	18	100.00	−51.77	−48.02
R-HSA–190,375	Reactome Gene Sets	FGFR2c ligand binding and activation	12	66.67	−39.70	−36.91
WP4172	WikiPathways	PI3K-Akt signaling pathway	17	94.44	−31.94	−29.47
WP3932	WikiPathways	Focal adhesion: PI3K-Akt-mTOR-signaling pathway	16	88.89	−29.83	−27.42
WP4787	WikiPathways	Osteoblast differentiation and related diseases	11	61.11	−22.12	−19.75
R-HSA–190,377	Reactome Gene Sets	FGFR2b ligand binding and activation	6	33.33	−17.43	−15.08
GO:0070374	GO Biological Processes	positive regulation of ERK1 and ERK2 cascade	10	55.56	−16.83	−14.47
GO:0051216	GO Biological Processes	cartilage development	5	27.78	−7.54	−5.30
GO:0060445	GO Biological Processes	branching involved in salivary gland morphogenesis	3	16.67	−7.00	−4.80
GO:0046620	GO Biological Processes	regulation of organ growth	4	22.22	−6.46	−4.28
GO:1,901,215	GO Biological Processes	negative regulation of neuron death	3	16.67	−3.61	−1.61

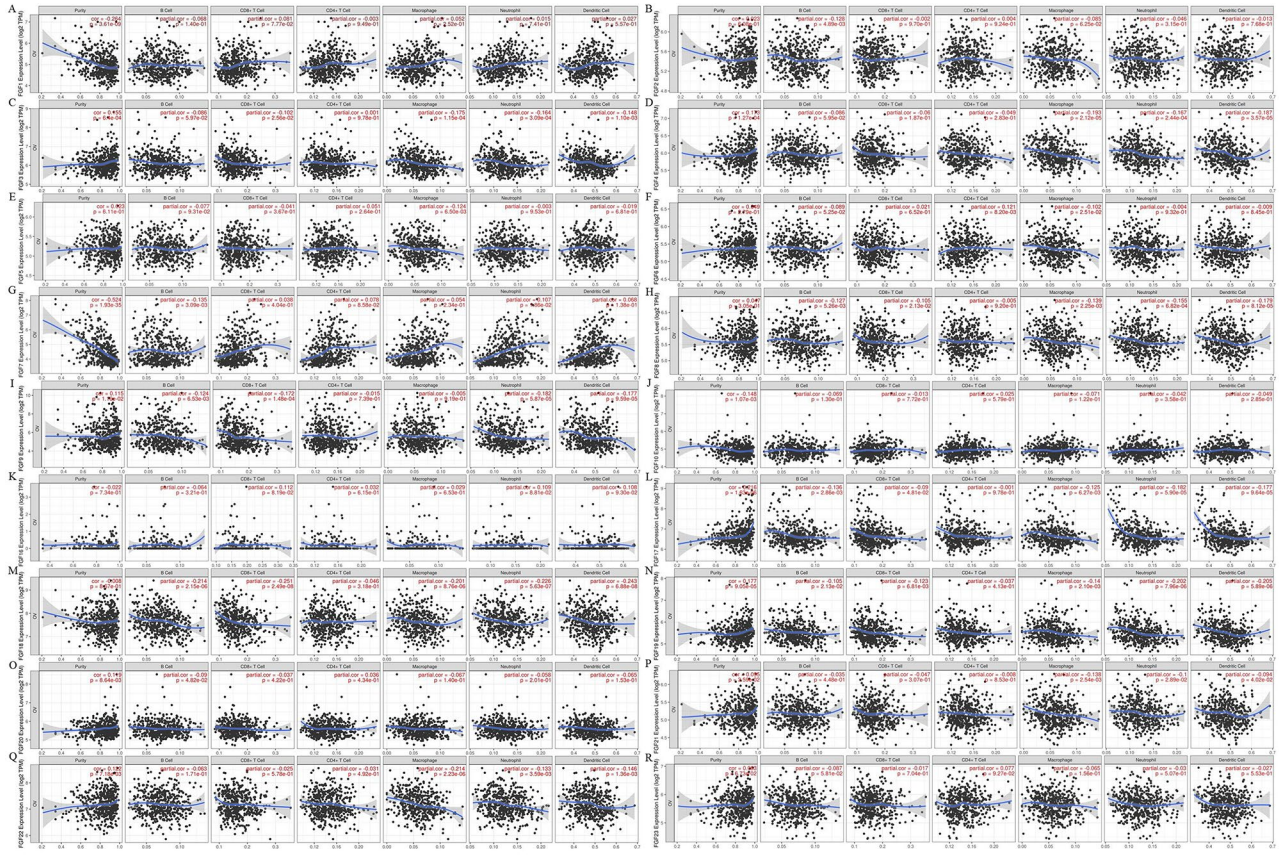


Fig. 7 The correlation between timmune infiltration level and the expression of (**A**) FGF1, (**B**) FGF2, (**C**) FGF3, (**D**) FGF4, (**E**) FGF5, (**F**) FGF6, (**G**) FGF7, (**H**) FGF8, (**I**) FGF9, (**J**) FGF10, (**K**) FGF16, (**L**) FGF17, (**M**) FGF18, (**N**) FGF19, (**O**) FGF20, (**P**) FGF21, (**Q**) FGF22, (**R**) FGF23 in OC. The gene expression levels against tumor purity are displayed on the left-most panel. The six subfigures on the right side of the tumor purity correlation plot show the specific relationship between specific immune cells and gene expression. The scatter plots display partially Spearman's rho values and statistical significance after purity correction

These findings imply that FGFs are crucial regulators of the OC pathway.

Discussion

In contrast to the apparent correlation between FGFs dysregulation and the development and spread of numerous cancers [19, 21, 35], the expression and functional significance of different FGFs in OC are yet unknown. This study is the first to use bioinformatics analysis to examine the transcriptional level, genetic variation, molecular mechanism, biological function, association with prognosis, and immune infiltration in OC patients.

All FGFRs can be activated by FGF1 [1], which activates a variety of cellular responses to be triggered and

Table 2 The cox proportional hazard model of FGFs and six tumor-infiltrating immune cells in OV (TIMER)

	coef	HR	95%CI_l	95%CI_u	*P*-value	sig
B_cell	8.197	3629.954	0.157	8.41E + 07	0.110	
CD8_Tcell	−4.302	0.014	0.000	4.03E + 00	0.139	
CD4_Tcell	−14.472	0.000	0.000	3.20E−02	0.010	*
Macrophage	5.070	159.199	0.017	1.52E + 06	0. 278	
Neutrophil	14.332	1676061.116	2.224	1.26E + 12	0.038	*
Dendritic	−2.441	0.087	0.000	1.16E + 02	0.506	
FGF1	−0.052	0.950	0.707	1.28E + 00	0.731	
FGF2	0.102	1.107	0.775	1.58E + 00	0.576	
FGF3	−0.071	0.931	0.749	1.16E + 00	0.520	
FGF4	0.456	1.578	0.893	2.79E + 00	0.116	
FGF5	−0.567	0.567	0.103	3.12E + 00	0.514	
FGF6	2.988	19.839	0.000	1.32E + 08	0.709	
FGF7	0.247	1.280	0.983	1.67E + 00	0.067	
FGF8	−0.068	0.934	0.662	1.32E + 00	0.698	
FGF9	0.162	1.175	0.980	1.41E + 00	0.082	
FGF10	0.090	1.094	0.663	1.81E + 00	0.724	
FGF16	0.145	1.156	0.846	1.58E + 00	0.362	
FGF17	−0.010	0.990	0.860	1.14E + 00	0.891	
FGF18	−0.015	0.986	0.861	1.13E + 00	0.832	
FGF19	0.132	1.142	0.964	1.35E + 00	0.125	
FGF20	−0.065	0.937	0.651	1.35E + 00	0.727	
FGF21	−0.194	0.824	0.534	1.27E + 00	0.380	
FGF22	0.153	1.165	0.780	1.74E + 00	0.456	
FGF23	1.526	4.601	1.822	1.16E + 01	0.001	*

*$P < 0.05$

functions intracellularly to provide anti-apoptotic protection and encourage cell survival [36]. Amplification of FGF1 in OC tissues increases angiogenesis, stimulates cancer cells in an autocrine manner, and has an oncogenic effect, according to a study by Birrer et al. [37]. FGF1 is also important for prognosis in advanced serous OC [37]. The TCGA dataset used in this investigation showed that FGF1 expression in OC tissues was higher than in normal tissues, but not statistically significant. It's interesting to note that the expression of FGF1 in patients with OC was related to the stage of the tumor. In OC patients who were followed up for 200 months, Kaplan-Meier plotter analysis showed that high FGF1 transcription level was linked with poor RFS and OS, which looked compatible with the role of FGF1 as a tumor suppressor. In previous studies, FGF-1/FGFR4 signaling activates the MAPK signaling pathway and is involved in ovarian tumorigenesis [38]. In our study, the FGF-1 mRNA levels in ovarian tumor tissues were significantly increased compared with those in paired normal tissues, but these differences did not achieve statistical significance. It is important to note that the association between FGF1 mRNA expression and tumor stage was statistically significant. The higher stage expressed the higher levels of FGF1. Furthermore, our study demonstrated that higher FGF1 mRNA levels was correlated with poor prognosis of patients with OC, in both OS and RFS. These observations are in agreement with the prior conclusion that FGF1 is a major prognostic factor in ovarian tumorigenesis.

Among the FGFs, FGF2 is the most widely studied in OC [23]. FGF2 has strong angiogenic activity and is thought to be a proponent of tumor angiogenesis, it exerts its biological effects through contact with FGFR1 [39]. Several OC cell lines exhibit FGFRs, and in vitro studies have shown that FGF2 promotes their proliferation [23]. FGF2 has also been demonstrated to make some OC cells more susceptible to the chemotherapy drug cisplatin [23]. In OC cells, FGF2 cytoplasmic concentrations greater than 500 pg/mg were linked to better overall survival [40].

FGF3 is not present in healthy tissues but is expressed in cancerous cell lines and tumor tissues [1]. Although the study discovered that 20% of OC samples had an amplified FGF3 oncogene, it did not discover any effects of FGF3 copy number on OS [9]. According to the findings of our investigation, the expression of FGF3 in OC tissues was higher than that in normal tissues (with no significance), and survival analysis revealed a substantial correlation between higher levels of FGF3 expression and better RFS in OC patients.

The FGF4 gene participates in a number of biological functions for cells, including cell differentiation, morphogenesis, and proliferation [41]. The oncogenic role of FGF4 has been demonstrated [42, 43]. By acting on the

FGFR2 receptor, it promotes stem cell-like characteristics and carcinogenesis in OC [42]. Yang et al.revealed that although previous reports indicated significant amplification of the FGFR2 gene in gastric cancer, survival analysis in the GEPIA database revealed no significant difference between the group with mutations in the FGFR2 gene and the group without mutations [12]. Furthermore, Yang et al. also showed that FGF401(an FGFR4 inhibitor) could prevent the proliferation of FGFR4 overexpression in the gastric cancer mouse xenograft model. Although clinical studies of the FGFR family primarily focus on inhibiting FGFR2 in gastric cancer, it seems that FGFR4 may be another potential option for targeted therapy in the future [12]. Little is currently understood regarding FGF5's expression and function in OC. FGF5 is often overexpressed in embryonic tissues but is seldom overexpressed in adult tissues [44]. Overexpression of FGF5 in adult tissues has been linked to several cancers, including prostate, pancreatic, breast, and renal cell carcinomas [45]. In our study, Patients with OC who expressed more FGF5 had better OS.

FGF6 is normally expressed in skeletal muscle, but this protein was not found in normal breast or prostate tissue, whereas FGF6 is expressed in some breast cancers [46] and prostate cancers [47]. It is still unknown what function FGF6 expression plays in OC. Notably, patients with OC who have higher FGF6 expression had better RFS.

Several malignancies, including cervical cancer [10], gastric cancer [11], and breast cancer [13], are shown to have high levels of FGF7 expression. However, the expression of FGF7 in OC has yet to be investigated. In our study, we discovered that OC tissues had lower levels of FGF7 expression than normal tissues. In patients with OC, lower FGF7 expression is associated with better OS.

Several tumor types, including OC, prostate cancer, breast cancer, hepatocellular cancer, and colorectal cancer, have elevated levels of FGF8 [48]. This factor activates anti-apoptotic pathways and inhibits tumor cell death brought on by the IIIc splice version of FGFR1-3 and FGFR4 receptors [49]. Our investigation revealed that higher FGF8 transcription levels were linked to better RFS and OS in OC patients.

As an exosome-related gene, FGF9 was initially discovered in human glioma cells [50]. According to Rahul Bhattacharya et al.'s research, OC tissues had higher levels of FGF9 expression, and FGF9-mediated OC cell invasion was linked to a metabolic shift of cells towards increased aerobic glycolysis [51]. However, the findings of our investigation revealed that association between high FGF9 transcription and worse RFS and OS in OC patients suggests that FGF9 has an oncogenic function in OC.

Prostate, breast, and pancreatic ductal adenocarcinomas are malignancies that are associated with FGF10 [17, 52]. FGF10, which primarily functions through FGFR2b and FGFR1b [17], can promote cancer cell proliferation by increasing the G1 to S phase transition and getting cells ready for synthesis and mitosis [53]. Activated FGFR2 activates downstream signaling pathways via PI3K-AKT or RAS-MAPK, which promotes cell proliferation [17]. In our study, we showed that FGF10 expression was lower in OC tissues than in normal tissues. It's interesting to note that higher FGF10 transcription was linked to lower RFS in OC patients.

Human embryonic carcinoma cells' ability to survive can be increased by FGF16 [54], and OC can be accelerated by WNT signaling with FGF16. A higher FGF16 transcription was associated with better RFS and OS in OC patients. FGF17 is a secreted growth factor [55] and is widely expressed in the endometrium, thyroid, brain, adrenal gland, and spleen [17]. Multiple malignancies, including prostate cancer [56], lung cancer [57], and acute leukemia [17], exhibit high levels of FGF17 expression. In acute leukemia, overexpression of FGF17 was significantly linked to a poor prognosis [17]. However, the prognostic role of FGF17 in OC has not been investigated. We discovered that FGF17 expression was lower in human OC than in normal tissues. In OC patients, higher FGF17 expression was linked to better RFS.

Notably, of all FGFs FGF18 may be the most important for suggesting OC prognostic outcomes. FGF18, a mitogenic, chemotactic, and angiogenic factor, plays a key role in accelerating the development of ovarian high-grade serous carcinoma [58, 59]. By activating NF-B and consequently increasing the production of oncogenic cytokines and chemokines, FGF18 regulates the migration, invasion, and tumorigenicity of OC cells [60]. Additionally, it has been suggested that FGF18 overexpression is a solo predictor of a poor clinical outcome in OC patients [60]. We discovered that whereas FGF18 expression levels in human OC tissues were higher than in normal tissues, there is no relationship between this expression in OC patients and the stage of the tumor. Poorer OS was linked to increased FGF18 transcription in OC patients, which seems to be consistent with FGF18 as a tumor-promoting factor.

FGF19 is distinguished by its role as a hormone, which regulates the synthesis of bile acids and influences glucose and lipid metabolism [61, 62]. It's interesting to note that obesity and diabetes are thought to be positively related to OC risk [63, 64]. Through the AKT-MAPK signaling pathway, Hu L et al. showed that the FGF19-FGFR4 signaling pathway can encourage the growth and invasion of OC [22]. Furthermore, it is thought that OC patients with high FGF19 expression have a poor prognosis [22]. We discovered that FGF19 expression was significantly linked with tumor stage in OC patients and was higher (without significance) in normal tissues in human

OC. Furthermore, higher FGF19 transcription was linked to poorer RFS in OC patients.

The expression of FGF20 and FGF21 in OC, however, has not been studied. We discovered that human OC patients had lower levels of FGF20 expression and higher FGF21 expression than normal tissues. Interesting correlations between high FGF20 transcription and better OS were found in OC patients. Better RFS and OS were linked to increased FGF21 transcription in OC patients, which tended to support the tumor suppressor function of FGF21.

FGF22 is linked to ovarian and skin cancer [65, 66]. In OC, FGF22 alters the thyroid hormone system [65], and mice studies imply that FGF22 may have a pro-oncogenic effect on the skin [66]. We discovered that FGF22 expression in human OC was lower than in normal tissues. In OC patients, higher FGF22 transcription was linked to better OS.

In comparison to women with early-stage OC or benign disease or in healthy women, serum or plasma concentrations of FGF23 were significantly higher in women with advanced OC [23]. The elevated serum concentrations of FGF23 are caused by tumor production and release of this protein [23]. It is interesting to note that higher FGF23 transcription was associated with better RFS and OS in OC patients.

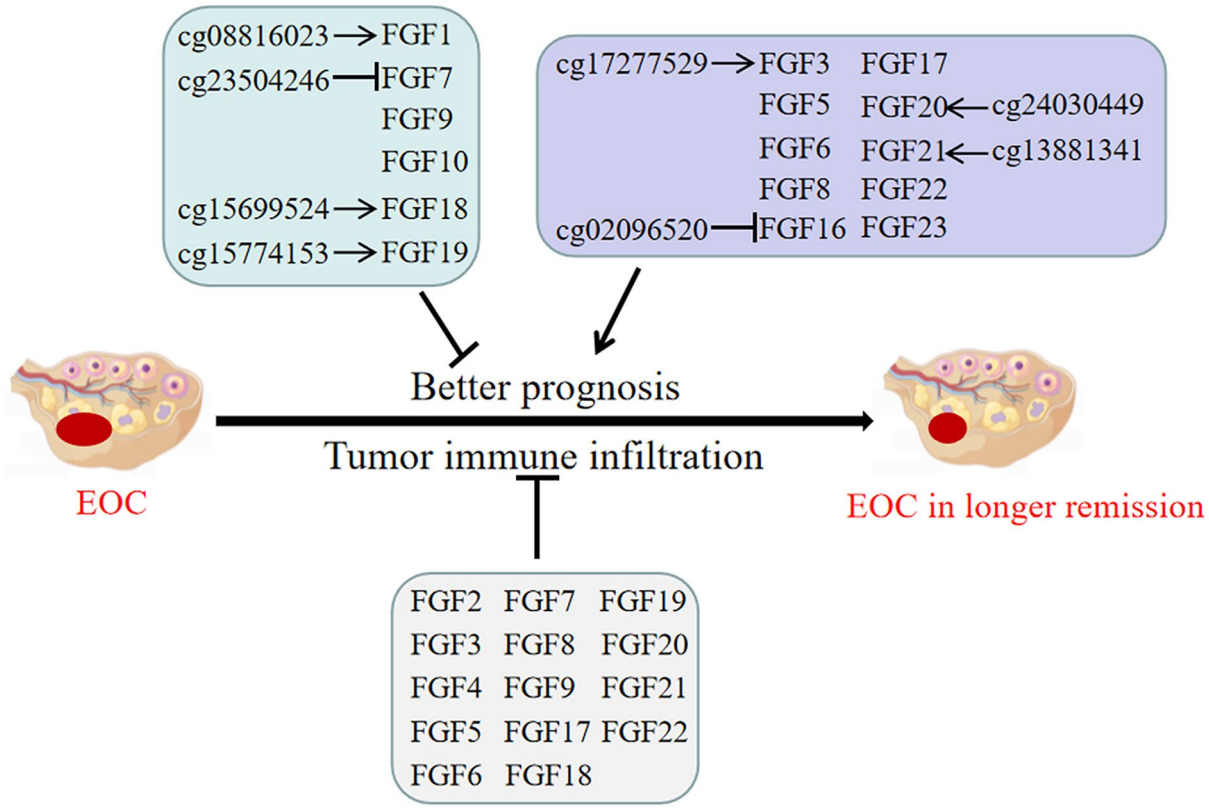
Although structurally related, FGF1, FGF18, and FGF19 belong to different FGF subfamilies and exhibit different modes of action, secretion mechanisms, and ultimate biological consequences. FGF1, FGF18 and FGF19 belong to the FGF1 subfamily (FGF1/2), the FGF8 subfamily (FGF8/17/18), and the FGF19 subfamily (FCF19/21/23), respectively [6]. Despite these differences, FGF1, FGF18, and FGF19 show consistency as prognostic/predictive biomarkers of OC.

DNA methylation influences cell differentiation and is involved in the development of tumors [67]. Keita et al. [68] discovered noticeably aberrant DNA methylation linked to tumor aggressiveness and serous OC development. Li et al. [69] discovered a correlation between platelet coagulation/parametric factor levels and the DNA methylation status of peripheral blood leukocytes in epithelial OC. Here, we found a potential link between OC patients' FGF expression and FGFs methylation levels. The potential contribution of FGFs DNA methylation to OC cancer requires more proof.

Our genetic study revealed that the differentially expressed FGFs in OC patients had a high mutation rate (40.19%), and these relationships between the differentially expressed FGFs and the OC may be mutually exclusive or synergistic. Additionally, we built a GGI network comprising the FGFs and the neighboring genes and discovered that these genes were most associated with the cellular response to FGF stimulation. Then, using enrichment analysis, we analyzed the role of FGFs and the proteins that surround them. Studies have found that the functions of FGFs are mainly related to the activated point mutants of FGFR2, fibroblast growth factor receptor signaling pathway, FGFR2c ligand binding and activation, PI3K-Akt signaling pathway, FGFR2b ligand binding and activation and positive regulation of ERK1 and ERK2 cascade. Eight FGF genes (FGF1, FGF2, FGF5, FGF7, FGF9, FGF17, FGF18, and FGF20) were found to be significantly involved in OC-related signaling pathways, including apoptosis, cell cycle, DNA damage response, EMT, hormone AR, hormone ER, PI3K/AKT, RAS/MAPK, and RTK pathways, according to the related pathways network. These pathways play a crucial role in the emergence and progression of OC. Another important finding of this study is the strong correlation between the transcriptional levels of FGFs and the different levels of immune infiltration in OC, which raises the possibility that FGFs play a role in the regulation of OC tumor immunity.

In our investigation, the mRNA expression levels of some FGFs in OC were positively correlated with protein expression. However, some FGFs mRNA expression levels were negatively correlated with protein expression. This inconsistency may be caused by the fact that there are multiple levels of regulation of gene expression; transcriptional regulation is only one of these levels; additional components include post-transcriptional regulation, translational regulation, and post-translational regulation, all of which contribute to the expression of the final protein. However, our study does have some limitations. Firstly, each dataset we utilized contains inherent bias. Secondly, follow-up mechanistic studies and in vivo and vitro experiments are necessary to validate our findings. Future research directions have been identified by addressing gaps in our current understanding. By integrating information from Cross-omics research, we can achieve a more comprehensive understanding of the complexity involved in gene expression regulation and identify potential post-transcriptional and post-translational regulatory mechanisms. Expanding the sample size and data coverage enables us to uncover hidden patterns and trends within large-scale data. Through functional research and validation, we can unravel the mechanisms of action in cellular and biological processes. Furthermore, by constructing and analyzing more complex networks and pathways, we can predict potential regulatory mechanisms and biological functions.

In conclusion, our study gained insight into the effect of FGF expression on OC prognosis and tumor immunity (Fig. 8). According to our findings, the enhanced expression of FGF1/18/19 in OC tissues may be crucial to the development of OC, and as a molecular marker, the high expression of FGF1/18/19 can also be used to identify



	IIIb			IIIc			
Receptor	FGFR1	FGFR2	FGFR3	FGFR1	FGFR2	FGFR3	FGFR4
Ligand	FGF1	FGF1	FGF1	FGF1	FGF1	FGF1	FGF1
	FGF2	FGF3	FGF8	FGF2	FGF2	FGF2	FGF2
	FGF3	FGF4	FGF9	FGF4	FGF4	FGF4	FGF4
	FGF8	FGF7	FGF16	FGF6	FGF6	FGF5	FGF6
	FGF9	FGF9	FGF18	FGF8	FGF8	FGF6	FGF8
	FGF10	FGF10		FGF16	FGF9	FGF8	FGF17
	FGF20	FGF21		FGF17	FGF16	FGF9	FGF19
	FGF21	FGF22		FGF20	FGF17	FGF16	
	FGF22			FGF21	FGF21	FGF17	
				FGF23	FGF23	FGF18	

Fig. 8 Abstract-based lines of research. Effect of FGF expression on OC prognosis and tumor immunity. FGF/FGFR binding specificity is also shown. EOC: epithelial ovarian cancer

high-risk subgroups of OC patients. Furthermore, the inconsistent correlation between mRNA and protein expression levels of FGFs underscores the need for further investigation into post-transcriptional and post-translational regulatory mechanisms.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
All authors read and approved the final version of the manuscript. Y.W., H.Z., and Y.Z. proposed the idea, drafted the manuscript. Z.L., S.L., and S.G. checked the integrity and plausibility of data analysis. S.G. revised the manuscript and

was responsible for the integrity of data acquisition and statistical analyses. Y.W., S.G.verified the underlying data.

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Data availability
All data about the patients can be found in the TCGA database. https://www.cancer.gov/ccg/research/genome-sequencing/tcga. All data of Proteomics can be found in the Human Protein Atlas. https://www.proteinatlas.org/. All data in this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate
This article does not include any studies conducted by any of the authors on human participants.

Consent for publication
Not applicable.

Competing interests
The authors confirm that there are no known conflicts of interest associated with this publication.

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