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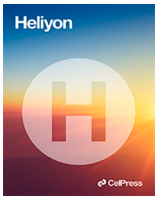

Research article

Increased FGF2 expression promotes immune cell infiltration and correlates with an unfavorable prognosis in thyroid cancer

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ABSTRACT

To delve into the expression and functions of FGF2 in patient with thyroid cancer (THCA), we conducted a systematic analysis of the association of FGF2 with immune cell infiltration, and prognosis in THCA patients. The transcription and protein levels, methylation, and biological properties of FGF2 were examined, along with its correlation with prognosis and immune cell infiltration in THCA patients using online databases UALCAN, Human Protein Atlas, Kaplan-Meier Plotter, DNMIVD, cBioPortal, GEPIA, Metascape, Linkedomics and TIMER. Clinical samples were collected for Western blot analyses. FGF2 was substantially overexpressed in the tumor group and shown correlations with age, tumor histology, nodal metastasis, and cancer stages. Moreover, higher expression of FGF2 *(HR = 3.42, 95 % CI:1.57-7.44, p = 0.00099)* was greatly correlated with poorer relapse-free survival in THCA patients, particularly in female patients. FGF2 methylation level was increased in the tumor group *(p = 1.29E-6)*, and higher methylation levels of FGF2 were positively correlated with the poorer progression-free interval in THCA patients *(p = 0.015)*. FGF2 mutations were markedly associated with shorter disease-free survival, with a mutation rate of 6 % among the total 498 THCA patients. FGF2 functions were potentially related to cell adhesion, cytokine-cytokine receptor interaction and angiogenesis. FGF2 expression showed positive correlations with the infiltration of B cells *(Cor = 0.569, p = 1.04e-42)*, $CD4^+$ T cells *(Cor = 0.555, p = 9.43e-41)*, macrophages *(Cor = 0.438, p = 2.94e-42)*, neutrophils *(Cor = 0.578, p = 9.354e-45),* and dendritic cells *(Cor = 0.591, p = 5.00e-47)*. FGF2 is a potential prognostic marker in THCA patients, with its functions possibly related to cell adhesion, interaction of the cytokine-cytokine receptor, angiogenesis, and the promotion of multiple immune cell infiltration.

1. Introduction

Thyroid cancer (THCA) is recognized as a prevalent endocrine malignancy [1,2], with rising incidence in recent years and a notable annual growth rate of around 20 % in China [3]. The incidence and mortality of THCA vary according to differences in race, genetics, environmental, and individual factors [4]. However, the precise mechanisms underlying the pathogenesis of THCA are still unclear. Thus, it is crucial to explore the etiology and identify effective prognostic indicators for THCA.

Recent research has highlighted the significance of fibroblast growth factor 2 (FGF2) in the pathogenesis, progression, invasion,

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and prognosis of cancer patients. Wang et al. discovered a positive correlation between increased FGF2 expression and advanced clinical stage in ovarian cancer, as well as a negative correlation with tumor differentiation [5]. Rasmuson et al. reported that higher FGF2 levels were connected with significantly poorer prognoses in renal cancer patients [6]. However, the function of FGF2 in THCA occurrence, development, and prognosis and its potential mechanisms remains largely elusive.

With advancements in RNA sequencing and microarray technology, DNA and RNA studies have been an indispensable part in the biological and biomedical fields. In this study, we aimed to illustrate the functions and prognostic power of FGF2 in THCA patients. The expression level, methylation, mutation, and potential pathways of FGF2, and its association with immune infiltration were studied, to enhance our understanding of the roles of FGF2 and improve the prognosis of THCA patients.

2. Materials and Methods

2.1. UALCAN

UALCAN (http://ualcan.path.uab.edu/analysis.html), an interactive Web resource, was employed to analyze cancer omics data from TCGA database [7]. "Scan my genes" and "Expression Analysis" modules of UALCAN were utilized to retrieve FGF2 mRNA data in diverse cancers, including THCA tissues and normal tissues.

2.2. Human Protein Atlas

Human Protein Atlas (https://www.proteinatlas.org) is a valuable web for mapping human protein data through immunohistochemical image, antibody-based imaging, and mass spectrometry-based proteomics [8]. FGF2 protein levels in both THCA tissues and normal thyroid tissues were compared using immunohistochemical image.

2.3. Kaplan-Meier Plotter

The Kaplan-Meier (K-M) plotter (http://kmplot.com/analysis) was applied for assessing the correlation between FGF2 expression and THCA patient survival. GEO, EGA, Impact, Metabric, TCGA databases and PubMed repositories were adopted [9]. 502 cancer patients were assigned into high and low groupsbased on the median expression.

2.4. DNA methylation interactive visualization database (DNMIVD)

DNMIVD (http://119.3.41.228/dnmivd/index/) incorporates high-throughput microarray data from TCGA and GEO databases [10]. In this study, the differential methylation levels and their impacts on the progression-free interval (PFI) of FGF2 in were detected in both THCA tissues and normal tissues.

2.5. cBioPortal

cBioPortal (https://www.cbioportal.org) is platform designed to analyze cancer genomics data from TCGA database [11]. In our study, 498 THCA samples were harvested from TCGA and PanCancer Atlas, and their mRNA expression z scores were collected via a z score threshold of ± 1.8 using RNA Seq V2 RSEM. The information about genetic alterations and disease-free survival (DFS) of FGF2 was analyzed.

2.6. GEPIA2 dataset

GEPIA2 (http://gepia.cancer-pku.cn/index.html) is to analyze the RNA sequencing data from TCGA and GTEx projects [12]. The "similar genes" module of GEPIA2 was utilized to obtain the top 50 genes similar to FGF2 for further analysis. "Survival Analysis" module was adopted to explore the prognostic value of FGF2 expression.

2.7. Metascape

Metascape (http://metascape.org) is utilized for gene annotation and enrichment analysis [13]. "Custom Analysis" module of Metascape was utilized to analyze the functions of the top 50 genes similar to FGF2 obtained in GPEIA. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were done to determine the biological processes, cellular components, molecular functions, and pathways related to these similar genes. Significance was determined based on a minimum overlap of 3, p-value <0.05, and enrichment factor >1.5.

2.8. LinkedOmics

LinkedOmics (http://www.linkedomics.org) provides multi-omics data from 32 types of cancer [14]. "LinkInterpreter" module was applied for Gene Set Enrichment Analysis (GSEA) on TCGA-THCA RNAseq data. The analysis was conducted with a minimum gene set size of 3 and 500 simulations.

2.9. TIMER

TIMER (https://cistrome.shinyapps.io/timer) is applied for systematic analysis of immune infiltration in different cancers from TCGA database [15]. The abundances of B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages and dendritic cells were assessed. The correlation between FGF2 expression and immune infiltration was explored using the "Gene module".

2.10. Collection of clinical samples

Three pairs of THCA tissues and adjacent non-tumor tissues were collected from THCA patients after surgical treatment in the Affiliated Hospital of Qingdao University from April 2023 to August 2023. The tissue samples were promptly frozen in liquid nitrogen and stored at −80 °C.

2.11. Western blot

Total protein was extracted from tissues with RIPA, then electrophoresed, and moved to a PVDF membrane (Millipore, USA). The membrane was sealed using 5 % skim milk powder after 2 h. The samples were then incubated with primary antibody (BOSTER, BA14189, 1:1000) at 4 °C overnight and matched secondary antibody for 1.5 h the next day. Finally, the samples were exposed, with GAPDH as a control gene.

2.12. Statistical analysis

All data analyses were done using online bioinformatics databases between April 15 and April 20, 2023. The differential transcriptional expression level of FGF2 was assessed using the Student's t-test. K-M survival curves and hazard ratio (HR) with 95 % confidence intervals (CI) and log-rank tests were performed to assess overall survival (OS), relapse-free survival (RFS), and DFS in different groups. Spearman's correlation analysis was employed to determine the relationship between FGF2 and potential pathways. $P < 0.05$ implied significant differences.

3. Results

3.1. Overexpression of FGF2 in THCA patients

To identify the prognostic power of FGF2 in THCA patients, mRNA expression was analyzed using the UALCAN database, FGF2 mRNA expression was measured in 24 t types of cancer (Fig. 1). The average FGF2 mRNA expression in the normal group and THCA group was 1.741 and 2.696 transcripts per million, respectively. This result indicated that FGF2 was overexpressed in the THCA group (Fig. 2A, Table 1, $p = 9.99E\text{-}16$).

3.2. Association between FGF2 mRNA expression and clinical parameters of THCA patients

We tested the relationship between FGF2 mRNA expression and various clinical parameters of THCA patients, including sex, age, tumor histology, nodal metastasis status, and cancer stages. FGF2 mRNA expression did not significant differ based on gender (Fig. 2B–F), However, it showed correlations with age, tumor histology, nodal metastasis, and cancer stages. FGF2 mRNA expression in the 20-40Yrs group ($p = 0.006$) and the 41-60Yrs group ($p = 0.04$) was notably higher than in the 61-80Yrs group. FGF2 mRNA expression was notably higher in patients with classical papillary carcinoma ($p = 9.51E\text{-}13$) and tall papillary carcinoma ($p = 3.52E\text{-}06$) than patients with follicular carcinoma. FGF2 mRNA expression in patients with nodal metastases was visibly higher than those

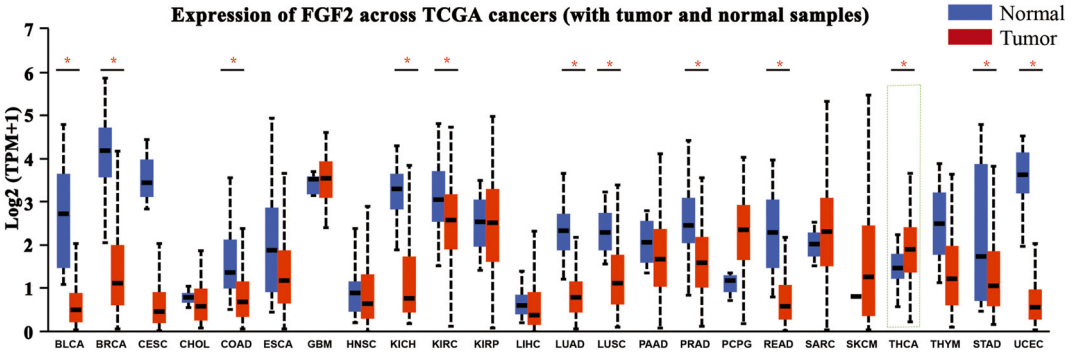


Fig. 1. Transcriptional expression of FGF2 in 24 different types of cancer diseases (UALCAN). *: p < 0.05, Compared to normal tissue, FGF2 expression was increased in several types of cancers, including thyroid cancer (THCA).

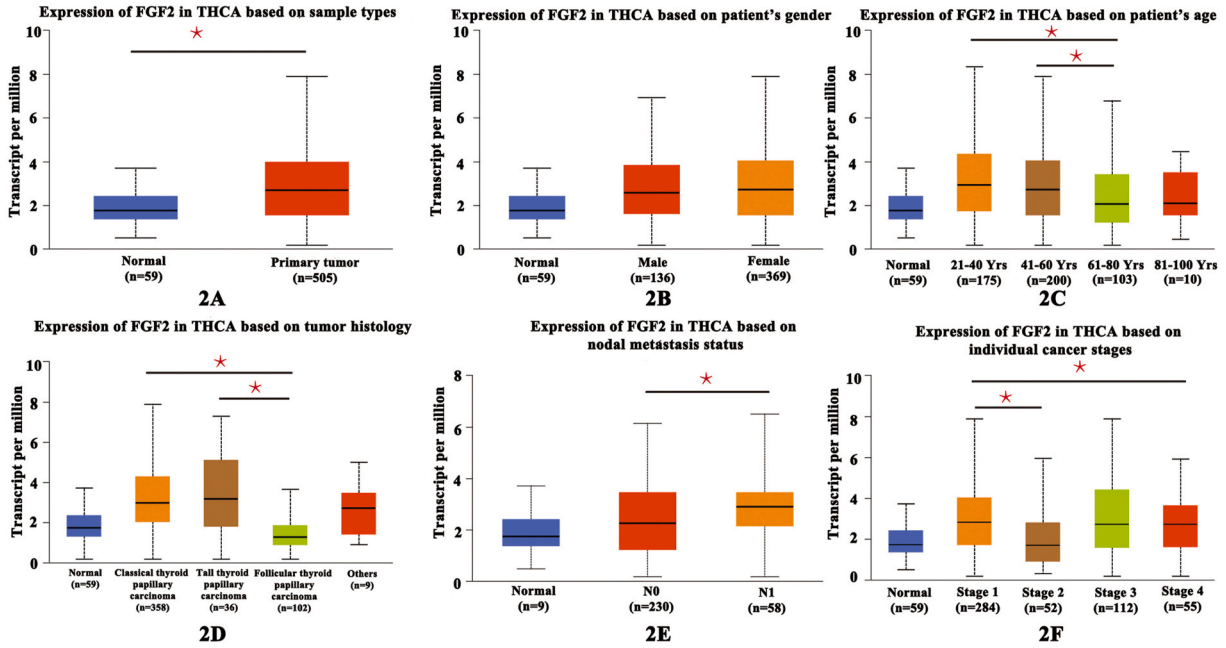


Fig. 2. Association between mRNA expression of FGF2 and clinical parameters (UALCAN). *: $p < 0.05$.
Compared to normal group, FGF2 expression was increased in THCA group (A). FGF2 expression did not show significant difference based on gender (B). FGF2 expression in the age groups 20-40Yrs and 41-60Yrs was significantly higher than in the 61-80Yrs group (C). FGF2 expression was significantly higher in patients with classical papillary carcinoma and tall papillary carcinoma than patients with follicular carcinoma (D). FGF2 mRNA expression was significantly higher in patients with nodal metastases than patients without lymph node metastases (E). FGF2 expression was significantly higher in stage I patients compared to stage II and IV patients (F).

Table 1
Transcriptional expression of FGF2 in THCA tissues and normal tissues (UALCAN database).

Group	n	Expression of FGF2 (Transcript per million)	P value
THCA	505	2.696 (1.567, 3.985)	9.99E-16
Normal	59	1.741 (1.35, 2.396)	

THCA: thyroid cancer.

without lymph node metastases *($p = 0.04$)*. FGF2 mRNA expression in stage I patients was greatly higher than that in stage II *($p = 0.027$)* and IV *($p = 0.026$)* patients (Table 2).

3.3. Protein expression of FGF2 in THCA tissue and normal tissue

FGF2 protein levels exhibited by immunohistochemical image were obtained from the Human Protein Atlas database. FGF2 protein level was low in normal thyroid tissue, whereas a medium level was observed in THCA tissue (Fig. 3A). Western blot demonstrated a considerable increase in FGF2 protein abundance in THCA tissues compared to the adjacent non-tumor tissues (Fig. 3B).

3.4. Prognostic power of FGF2 expression in THCA patients

GEPIA2 and K-M Plotter were adopted to explore the association between FGF2 expression and THCA patients prognosis. FGF2 expression was not correlated with OS (Fig. 4A and C) and DFS (Fig. 4B) in THCA patients. However, higher expression of FGF2 (*HR = 3.42, 95 % CI: 1.57-7.44, p = 0.00099)* was markedly correlated with a lower RFS in THCA patients, particularly in female patients (*HR = 3.78, 95 % CI: 1.55-9.26, p = 0.0017* (Fig. 4C–D).

3.5. Genetic methylation and FGF2 mutations and their associations with prognosis of THCA patients

We investigated the methylation and mutation status of FGF2 and their potential associations with prognosis in THCA patients using the DNMIVD and cBioPortal database. First, FGF2 methylation in THCA patients was prominently higher than the normal group (Fig. 5A, *p = 1.29E-6*). Furthermore, higher FGF2 methylation level was positively correlated with a poorer progression-free interval in

Table 2
Transcriptional expression of FGF2 in THCA patients with different clinical characteristics (UALCAN database).

Characteristics (n = 505)	n	Expression of FGF2 (Transcript per million)	P value
Sex			
Male	136	2.564 (1.604, 3817)	0.38
Female	369	2.719 (1.560, 4.032)	
Age			
21-40Yrs	175	2.923 (1.731, 4.329)	0.006
41-60Yrs	200	2.715 (1.559, 4.028)	0.04
61-80Yrs	103	2.053 (1.212, 3.413)	[a]
81-100Yrs	10	2.070 (1.566, 3.484)	0.618
Histological subtype			
Classical	358	2.976 (2.040, 4.275)	9.51E-13
Tall cell	36	3.187 (1.821, 5.107)	3.52E-06
Follicular	102	1.274 (0.890, 1.855)	[a]
Others		2.733 (1.428, 3463)	0.22
Stages			
I	284	2.827 (1.722, 4.014)	[a]
II	52	1.706 (0.929, 2.785)	0.027
III	112	2.733 (1.590, 4.392)	0.939
IV	55	2.757 (1.636, 3.635)	0.026
Nodal metastasis status			
N0	230	2.269 (1.216, 3.442)	0.04
N1	58	2.889 (2.142, 3.455)	

[a] :Means the data in the same clinical characteristics group were compared with it.

THCA patients (Fi. 5B, $p = 0.015$). FGF2 genes altered in 28 THCA patients, with a mutation rate of 6 % (Fig. 5C). FGF2 mutations were remarkably connected with a shorter DFS (Fig. 5D, $p = 0.0249$). These findings suggested that both FGF2 methylation and mutation status can impact the prognosis of THCA patients.

3.6. Predicted functions of FGF2 and the 50 most similar genes in THCA patients

The functions of FGF2 and the 50 closest genes were predicted by GO/KEGG enrichment analysis in Metascape. GO enrichment items were allocated into three categories: molecular functions (5 items), cellular components (2 items), and biological processes (9 items). The top 3 items in molecular functions included GO: 0001227 (DNA-binding transcription repressor activity, RNA polymerase II specific), GO: 0061629 (RNA polymerase II specific DNA-binding transcription factor binding) and GO: 0005516 (calmodulin binding). Cellular components included GO: 0090575 (RNA polymerase II transcription regulator complex) and GO: 0015629 (actin cytoskeleton). The top 4 items in biological processes included GO: 0006022 (aminoglycan metabolic process), GO: 0001525 (angiogenesis), GO: 0009100 (glycoprotein metabolic process), and GO: 0045087 (innate immune response) (Fig. 6A and B).

KEGG analysis identified 2 pathways including hsa04115 (p53 signaling pathway) and has05167 (Kaposi sarcoma-associated herpesvirus infection) associated with the functions of similar genes in THCA (Fig. 6C and D).

To clarify the association between FGF2 and THCA, a Metascape protein–protein interaction (PPI) enrichment analysis was performed. The PPI network was identified in the gene lists (Fig. 6E and F). The biological function was primarily related to the aminoglycan metabolic process, the cellular response to external stimuli, and angiogenesis.

3.7. GSEA analysis of FGF2 in THCA patients

To identify potential pathways correlated with high and low levels of FGF2 in THCA, RNA-seq expression-based GSEA was performed using Linkedomics. GSEA identified that high FGF2 expression was positively correlated with cell adhesion molecules (*normalized enrichment score (NES) = 2.167, FDR<2.2E-16*), cytokine-cytokine receptor interaction (*NES = 2.117, FDR<2.2E-16*), and osteoclast differentiation *(NES = 2.113, FDR<2.2E-16)* (Fig. 7).

3.8. Correlation between immune cell infiltration and FGF2 in THCA patients

FGF2 was involved in immune cell infiltration and inflammatory responses. Therefore, we evaluated the correlation between FGF2 and immune cell infiltration using the TIMER database. FGF2 expression was positively correlated with the infiltration of B cells *(Cor = 0.569, p = 1.04e-42)*, $CD4^+$ T cells *(Cor = 0.555, p = 9.43e-41)*, macrophages *(Cor = 0.438, p = 2.94e-42)*, neutrophils *(Cor = 0.578, p = 9.354e-45)* and dendritic cells *(Cor = 0.591, p = 5.00e-47)*. However, there was no significant correlation with $CD8^+$ cell infiltration *(Cor = -0.06, p = 0.16)* (Fig. 8).

4. Discussion

Recent studies have increasingly recognized that FGF2 acts as a promising biomarker for predicting tumor prognosis in various

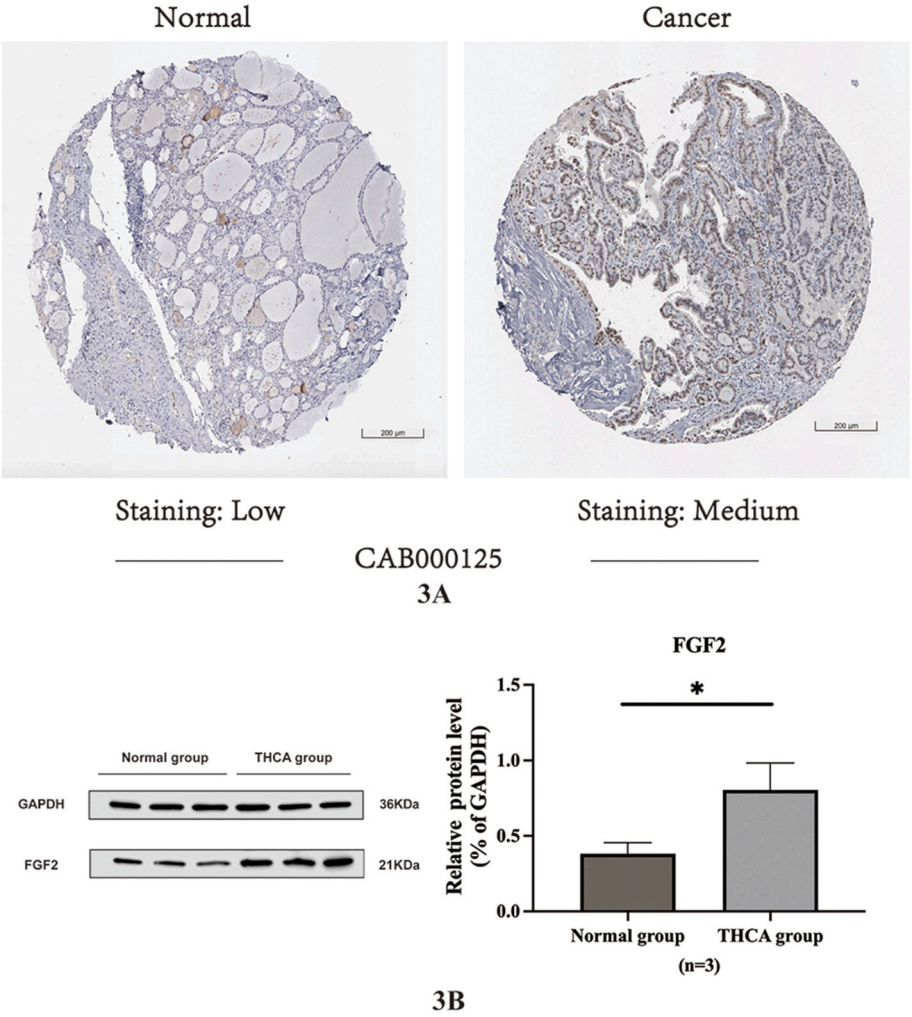


Fig. 3. Protein expression patterns of FGF2 in THCA tissue and normal thyroid tissue.
FGF2 expression was low in normal thyroid tissue, and was medium in THCA tissue (Human Protein Atlas). Protein level of FGF2 was elevated in THCA patients measured by Western blot (3B).

cancers [16]. However, the specific role of FGF2 as a prognostic biomarker in THCA has not been fully established. This paper illustrated that FGF2 was elevated in THCA tissue and higher FGF2 expression was associated with poor RFS in THCA patients. Its molecular functions may be related to cell adhesion, interaction of the cytokine-cytokine receptor, angiogenesis, and multiple immune cell infiltration.

We observed that FGF2 was elevated in THCA and was correlated with lymph node metastasis, consistent with previous reports. Han et al. discovered that increased expression of FGF2 mRNA in THCA tissues was associated with central lymph node metastasis, demonstrating that high FGF2 expression could be a risk index for proliferation, metastasis, and invasion of THCA [17]. Boelaert et al. reported that FGF2 mRNA expression showed a 5.0-fold increase in THCA compared to normal thyroids. High FGF2 expression was independently correlated with lymph node invasion [18]. Additionally, Li et al. determined that FGF2 expression was raised in THCA compared to normal tissue, and demonstrated a positive linear correlation between FGF2 expressions and lymph node metastasis [19].

Until now, studies have indicated that many variables are closely related to THCA prognosis. This study unveiled that overexpression of FGF2 *(HR = 3.42, 95 % CI: 1.57-7.44, p = 0.00099)* was substantially correlated with poorer RFS in THCA patients. FGF2 expression did not differ significantly by sex, while it was correlated with age, tumor histology, and individual cancer stages. Li et al. confirmed a positive linear correlation between FGF2 expressions and differentiation in papillary THCA, while there was no correlation with gender and age [19]. The non-correlation between FGF2 and age may be caused by different distribution and grouping by age of subjects in different studies. Grani et al. determined that many risk factors, including older age, stage, angioinvasion, distant metastases, and extrathyroidal invasion are independent survival predictors [20]. Han et al. discovered that age, pathological type, clinical stage, cervical lymph node metastasis, and distant metastasis were influencing factors for 5-year survival of THCA patients [21]. However, it should be considered whether these related factors influence FGF2 expression and the prognosis in THCA patients in

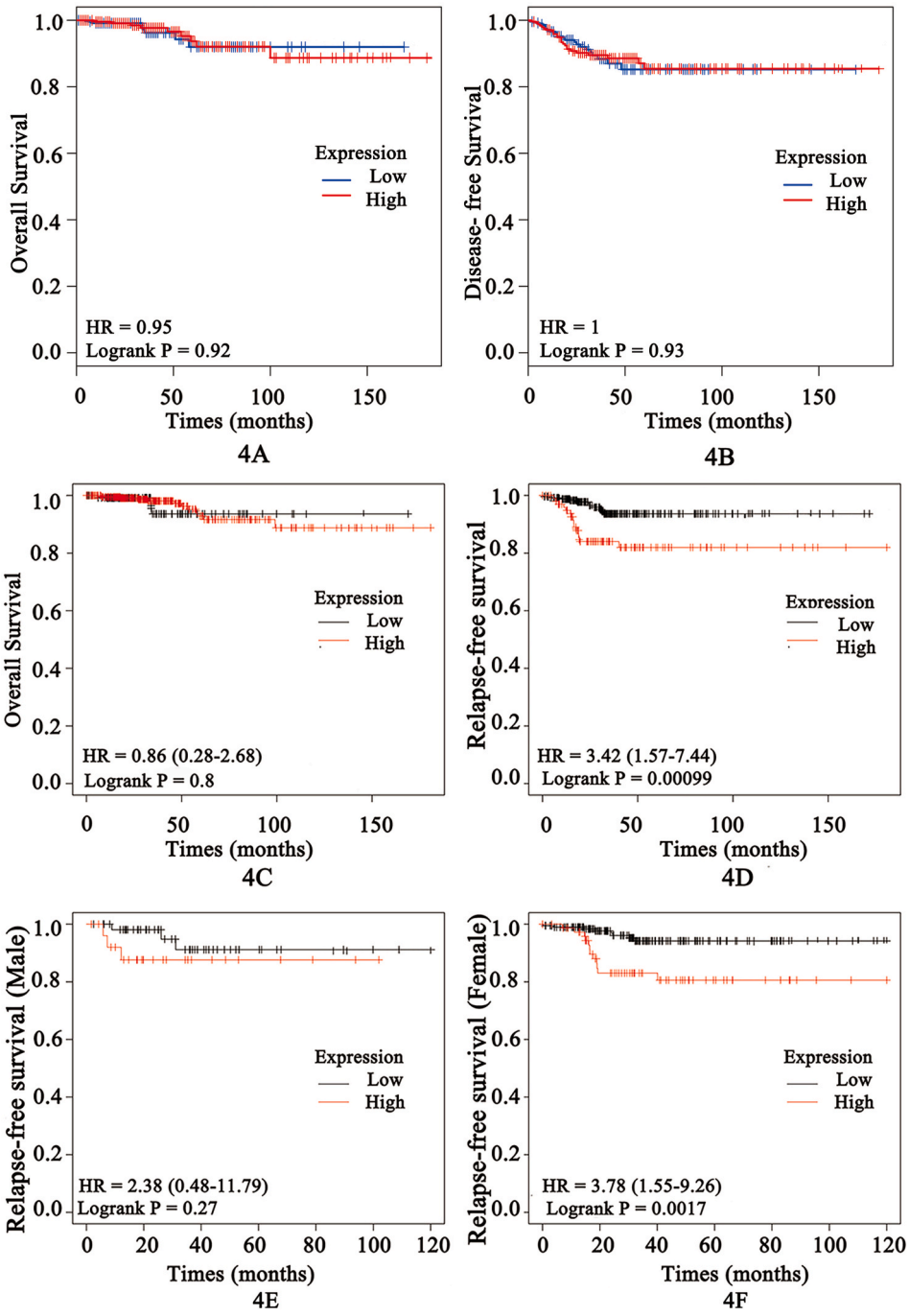


Fig. 4. Prognostic value of FGF2 mRNA expression in THCA patients (K-M Plotter).
The expression of FGF2 was not correlated with overall survival (OS) (4A and 4C, from GEPIA2 and KM Plotter databases) and disease-free survival (DFS) (4B, from GEPIA2 database) in THCA patients. Higher expression of FGF2 was significantly correlated with a lower RFS (relapse-free survival) in THCA patients (4D), especially in female patients (4E-4F, from K-M Plotter databases).

future studies.

FGF2, a member of the FGF family, acts in conjunction with FGFRs to regulate diverse cellular processes, like proliferation, apoptosis, migration, invasion, and angiogenesis [22]. Dysregulation of the FGF/FGFRs pathway has been observed in a various tumor types and is important in tumor development by promoting tumor angiogenesis and directly stimulating tumor growth. Our study evinced that FGF2 was potent in initiating cancer within the tumor microenvironment. By interacting with FGFR and synergistically activating downstream pathways, FGF2 enhances THCA cell proliferation, facilitates cell adhesion to the extracellular matrix,

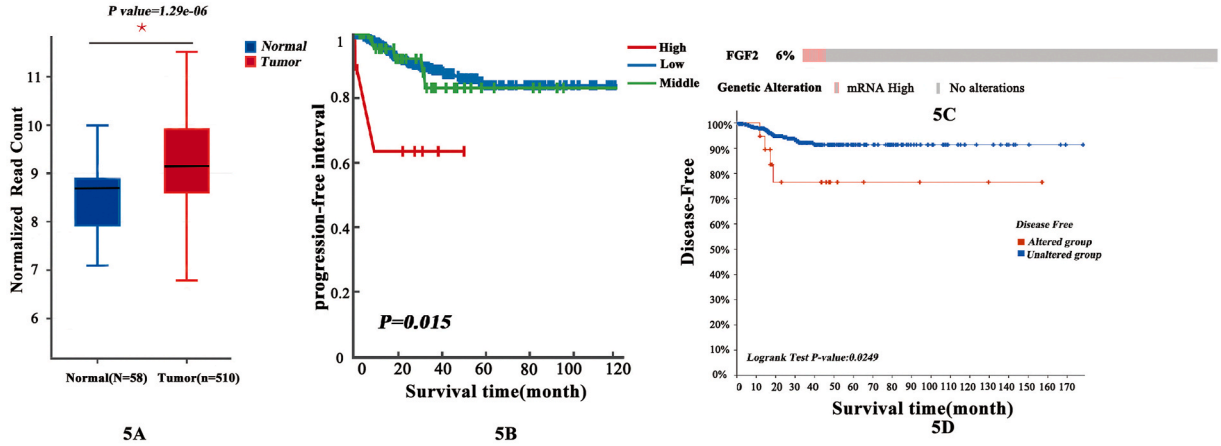


Fig. 5. Genetic methylation and mutations of FGF2 in THCA patients
The methylation level of FGF2 in THCA patients was significantly higher than that in normal group (A), high methylation level of FGF2 was positively correlated with a poor PFI in THCA patients (B). The mutation rate of FGF2 was 6 % in the total 498 THCA patients (C), FGF2 mutations were significantly associated with a shorter DFS (D).

promotes tumor-induced vasculature formation, and drives the infiltration of multiple immune cells. Huang et al. confirmed that FGF2 could promote THCA cell growth while inducing angiogenesis by modulating the release of inflammatory cytokines [23]. Yin et al. reported that miR-195 inhibited THCA cell migration and invasion by targeting FGF2. The miR-195-FGF2-MMP-13 axis may represent a novel target for addressing THCA metastasis [24]. Furthermore, Sheta et al. confirmed that chronic exposure to FGF2 can convert induced pluripotent stem cells into cancer stem cells, leading to autocrine cell growth and adhesion to the extracellular matrix, promoting proliferation, resulting in the accelerated growth of tumor mass [25]. However, current studies have not clarified the specific molecular mechanism of FGF2 upregulation in THCA tissues and how FGF2 facilitates THCA cell proliferation and invasion. Additional studies are needed to elucidate these mechanisms.

Immune cells are crucial in influencing the prognosis of THCA [26]. Fang et al. demonstrated that tumor-associated macrophages in the tumor microenvironment can promote THCA invasion through paracrine pathways [27]. Additionally, Yang determined that the clinical outcome of THCA patients could be improved by $CD8^+$ T cell infiltration [28]. Our study noted positive correlations between FGF2 expression and the infiltration of B cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells. These findings may offer potential insights into the immunotherapy of THCA.

In our study, the integrated analysis of multi-platform data with clinical data enhanced our understanding of the biological function of FGF2 in THCA. It may provide potential application of immunotherapy for THCA. However, there were still limitations. First, despite that FGF2 could be an independent prognostic factor in THCA, all data were mostly derived from publicly available databases, and the role of FGF2 as a novel prognostic marker in THCA is predominantly supported by K-M Plotter database. Further studies with large sample sizes are essential to validate our conclusions. Second, it remains unclear whether overexpression of FGF2 could be a diagnostic marker or therapeutic target for THCA. Additional studies are required for verification. Finally, the detailed mechanisms underlying the relationship between FGF2 and THCA still need further experimental exploration.

In conclusion, our study identified FGF2 as a potential prognostic marker for THCA patients, and its molecular functions may be related to cell adhesion, interaction of cytokine-cytokine receptor, angiogenesis, and multiple immune cell infiltration. These results provide a new guiding strategy for clinical treatment of THCA.

Data availability statement

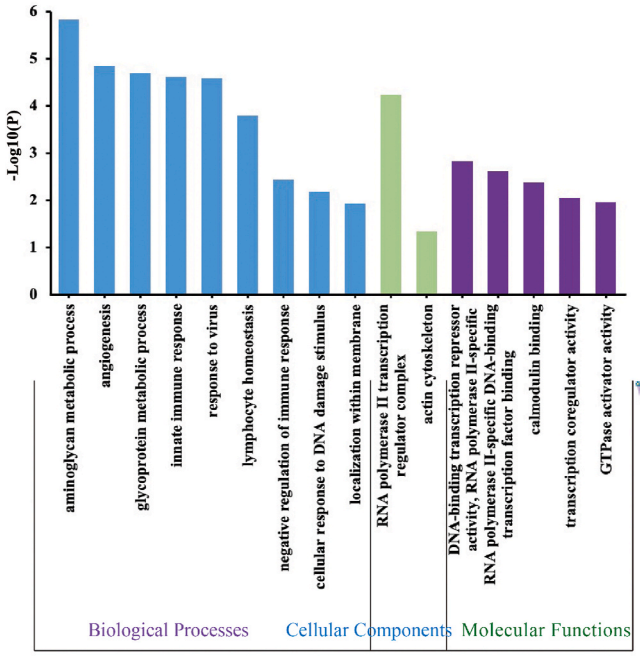
Data have been deposited into publicly available databases, including UALCAN, Human Protein Atlas, DNMIVD, Kaplan-Meier Plotter, cBioPortal, GEPIA2, Metascape, Linkedomics, and TIMER. The corresponding link to the databases can be found in the '**Materials and Methods'** section. We conducted this systematic analysis using all the databases. The accession number was no need.

Ethics declarations

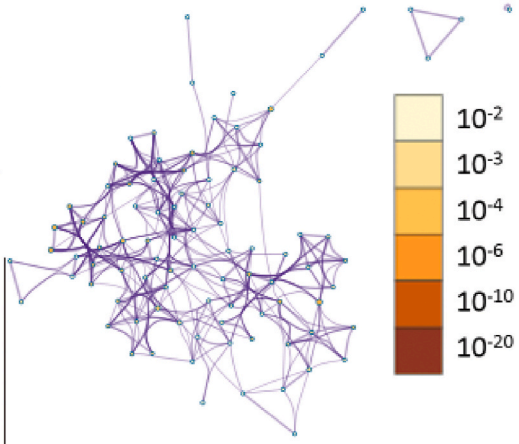
This study was ratified by ethics committee of Affiliated Hospital of Qingdao University, (QYFY WZLL 28300). All participants (or their proxies/legal guardians) provided informed consent to participate in the study.

CRediT authorship contribution statement

Han Chen: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Xiaoyun Du:** Methodology, Formal analysis.



6A



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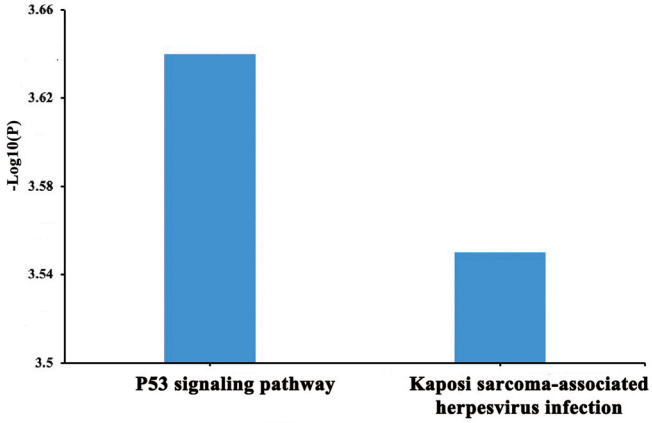

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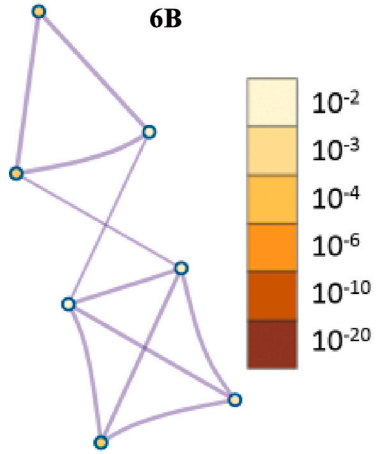

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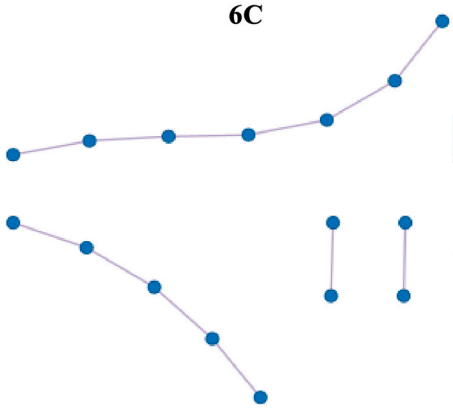

6E

GO	Description	Log10(P)
GO:0006022	aminoglycan metabolic process	-6.4
GO:0071496	cellular response to external stimulus	-6.3
GO:0001525	angiogenesis	-6.2

6F

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Fig. 6. Enrichment analysis of FGF2 and the top 50 similar genes in THCA patients (Metascape). Bar graph of GO enriched items colored by three groups based on their functions of biological processes (A). The network of GO enriched terms visualizes the relationships between these terms, with nodes representing different terms and the edges indicating connections between them. The color was set based on p-value, where terms with more genes are prone to have a more significant p-value (B). The bar graph of KEGG enriched items provides insights into the biological pathway tin which these genes are involved (C). The network of KEGG enriched terms illustrates the relationships between the enriched KEGG terms, with different colors indicating the significance of these terms based on their p-value (D). The PPI network and the significant three items indicate the specific proteins and interactions that play crucial roles in the network (E and F).

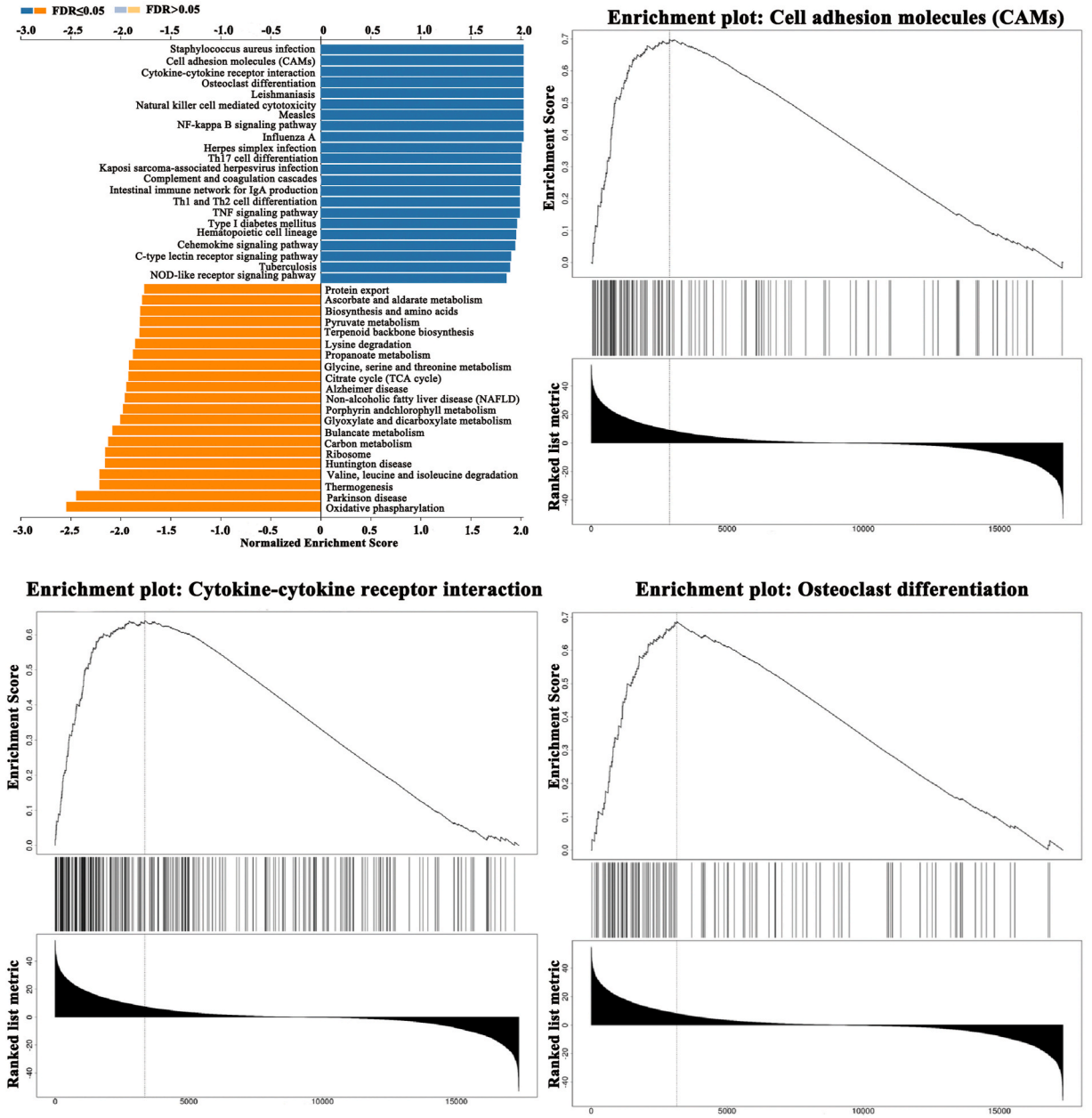

Fig. 7. GSEA analysis of FGF2 in THCA patients (Linkedomics).
A normalized enrichment score (NES) ≥ 0 indicates that the enrichment pathway is positively correlated with FGF2, and a false discovery rate (FDR) value ≤ 0.05 is considered statistically significant (A). High expression of FGF2 was positively correlated with cell adhesion molecules (B), cytokine-cytokine receptor interaction (C) and osteoclast differentiation (D).

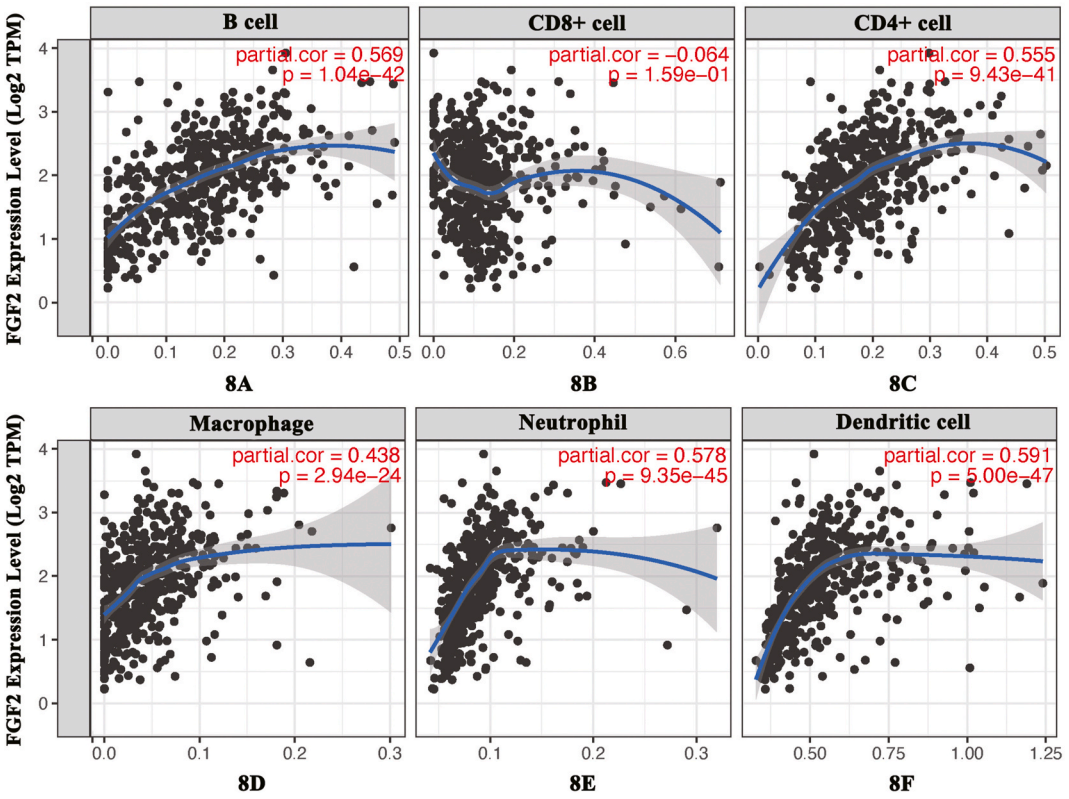

Fig. 8. The correlation between immune cell infiltration and FGF2 in THCA patients (TIMER). FGF2 expression was positively correlated with the infiltration of B cells (A), $CD4^+$ T cells (C), macrophages (D), neutrophils (E) and dendritic cells (F). There was no significant correlation with $CD8^+$ cell infiltration (B).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32272.

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