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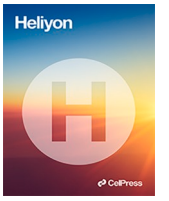

Research article

Pan-cancer analyses reveal genomics and clinical outcome association of the fatty acid oxidation regulators in cancer

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ABSTRACT

Background: Fatty acid oxidation (FAO) is considered to play a vital part in tumor metabolic reprogramming. But the comprehensive description of FAO dysregulation in tumors has not been unknown.

Methods: We obtained FAO genes, RNA-seq data and clinical information from the Msigdb, TCGA and GTEx databases. We assessed their prognosis value using univariate cox analysis, survival analysis and Kaplan-Meier curve. We determined the function of FAO genes using gene set variation analysis. The correlation analysis was calculated by corrplot R package. Immunotherapy response was assessed through TIDE scores. The protein expression levels of FAO genes were validated using immunohistochemistry (IHC).

Results: The FAO scores were highest in COAD but lowest in PCPG. FAO scores were significantly associated with the prognosis of some cancers in OS, DSS, DFI and PFI. Besides, gene set variation analysis identified that FAO scores were related to immune-related pathways, and immune infiltration analysis showed FAO scores were positively related to cancer-associated fibroblasts and various immune-related genes. TIDE scores were significantly decreased in ACC, CHOL, ESCA, GBM, LAML, SARC, SKCM and THCA compared with normal samples, while it was significantly increased in BLCA, LUAD, LUSC, PCPG, PRAD and STAD. Besides, most FAO genes were downregulated in pan-cancer compared with normal samples. Moreover, we found copy number variation (CNV) of FAO genes played a positive role in their mRNA expression, while methylation was negative. We determined FAO genes were closely related to some drugs in pan-cancer.

Conclusions: FAO score is a novel and promising factor for predicting outcomes.

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1. Introduction

Cancer is one of the leading causes of death worldwide [1]. With rapid population growth and aging, the cancer incidence rate will continue to increase over the next decades [2]. Numerous efforts have been made in cancer research, but challenges remain in many aspects, such as the etiology of cancer, the pathogenesis of cancer, the treatment of cancer, and so on.

Tumor cells demand more energy to maintain rapid proliferation and metastatic progression [3]. To meet the energy needs of cells, some oncogenes were activated and mutated to contribute to the metabolism reprogrammed [4], which has been well established as a characteristic of malignancies [5]. After numerous research, it has been proven that the common energy metabolism of tumor cells contained aerobic glycolysis and fatty acid oxidation (FAO) [6,7]. Moreover, recent studies reported that fatty acid oxidation (FAO) was dysregulated in diverse human cancers.

FAO is a multi-step catabolic process to convert long-chain fatty acids into acetyl-CoA. Acetyl-CoA will be fully oxidized through the electron transport chain and TCA cycle to generate ATP. Moreover, the number of ATP produced by FAO is several times more than the oxidation of glucose, thus, the promotion of FAO is meaningful for the development of tumor cells [4]. At present, emerging evidence has indicated that FAO is a promising target for cancer therapy. For example, some enzymes involved in the regulation of FAO progress are overexpressed in many types of cancers, which could associate strongly with poor outcomes for cancer patients [8,9]. In addition, the activated status of oncoproteins and the active oxidation of fatty acids may interact and promote each other [10,11]. Yet a comprehensive description of FAO in human pan-cancer remained uncharted territory. A full-scale study of FAO in pan-cancer will contribute to better understanding the molecular mechanisms involved in the development of malignancies and reveal new prognostic and therapeutic targets for cancer.

In the present research, we investigated the epigenome, transcriptome, and clinical information of patients in 33 cancer types from TCGA. We performed a comprehensive analysis of data at multiple aspects containing immune infiltration, prognosis and gene mutations. All these evidences provided that FAO might serve as novel prognostic biomarkers and therapeutic targets for pan-cancer.

2. Methods

2.1. Data collection

We got a FAO gene set from The Molecular Signatures Database (https://www.gsea-msigdb.org/gsea/msigdb/cards/GOBP_POSITIVE_REGULATION_OF_FATTY_ACID_OXIDATION) [12], including fifteen FAO related genes (PPARGC1A, CPT1A, MTLN, AKT2, ABCD1, FABP1, ABCD2, MLYCD, IRS1, PLIN5, PPARA, PPARD, TWIST1, NR4A3, and IRS2). RNA sequencing transcriptome data of TCGA and GTEx databases and clinical information were downloaded from the UCSC Xena database (https://xenabrowser.net/datapages/).

2.2. The landscape of FAO score in pan-cancer

The level of FAO score was quantified using the single-sample Gene Set Enrichment Analysis (ssGSEA) method by the "GSVA" package. We ranked 33 types of cancer according to their FAO scores and performed the "ggplot2" package to visualize the results.

2.3. Univariate regression analysis in pan-cancer

We employed the "survminer" and "survival" R packages to analyze the prognostic value of the FAO score. The log-rank P value, hazard ratio with 95% confidence intervals and log-rank *P*-value were also computed and exhibited. All the results were visualized as forest plots using the "forestplot" package in R.

2.4. Gene set variation analysis (GSVA)

The GSVA gene set (hallmark gene sets) was from the MSigDB database (v7.2 updated September 2020; https://www.gsea-msigdb.org/gsea/msigdb/index.jsp). Functional analysis was performed using the R-packages "limma", "GSEABase", "GSVA", and "ggplot2". After GSVA scores of all tumors were generated, the correlation between GSVA scores and FAO scores was computed, and the results were shown by the "pheatmap" package.

2.5. The analysis of immune infiltration in pan-cancer

Firstly, we conducted the "ESTIMATE" package in R to calculate TumorPurity, StromalScore, ESTIMATEScore and ImmuneScore values in each cancer and correlated these values with the FAO scores using the cor function. Besides, we used the methodology curated by Zeng D and colleagues [13] to investigate the correlation between the FAO score and other relevant biological processes.

Then, we obtained the information about immune infiltration in cancers based on the Immune Cell Abundance Identifier database (http://bioinfo.life.hust.edu.cn/ImmuCellAI#!/), which is a useful web server for systematical analysis of immune infiltrates across diverse cancer types. In addition, we used the "ggplot2" package to draw the correlation between the expression of immune-related gene sets and the FAO score.

2.6. The immunotherapy response predictions

Based on the mRNA expression profile, the Tumor Immune Dysfunction and Exclusion (TIDE) (http://tide.dfci.harvard.edu/) algorithm could be used to predict the potential of tumor immune escape of cancer samples.

2.7. Survival analysis

After the patients were divided into two groups, we used "survival" and "survimer" packages to assess the prognosis. Then, the survfit function was applied to calculate the risk and Hazard Ratio (HR) and fit the survival curve. Finally, the ggsurvplot R package was used to exhibit the results.

2.8. Validation of FAO-related gene expressions using immunohistochemistry (IHC)

The tumor sections were firstly soaked in xylene for 5 min followed by gradient alcohol hydration (100% for 10 min, 90% for 10 min, 70% for 10 min). After samples were washed three times with PBS for 3 min, they were flicked dry and put into a wet box. Then, 3% hydrogen peroxide was added in sections for incubation for 15 min at room temperature. After sections were washed three times with PBS for 3 min and flicked dry, they were incubated with 100 μL primary antibodies for 15 min in the dark at room temperature. Next, the sections were incubated with 100 μL secondary antibodies for 45 min at room temperature after they were washed three times with PBS for 3 min and flicked dry. The sections were color developed by 100 μL DAB working solution. Sections were counterstained with hematoxylin, differentiated with 0.1% alcohol hydrochloride and turned back to blue using 0.5% ammonia. The sections were dehydrated by graded ethanol (80% for 2 min, 95% for 2 min, 100% for 2 min) and cleared three times for 3 min with xylene and coverslipped before being visualized with an Olympus microscope. The information about all antibodies in this study was showed in Supplement Table 1.

2.9. The pan-caner analysis of single cell RNA (scRNA) data

Tumor Immune Single-cell Hub 2 (TISCH2) is a user-friendly, up-to-date and well-maintained data resource database for scRNA analysis and provides detailed cell-type annotation at the single-cell level. It includes 190 tumor scRNA-seq datasets covering 6 million cells in 50 cancer types, with 110 newly collected datasets.

2.10. Genetic mutations and methylation analysis of FAO genes in pan-cancer

GSCA database was a free, open and integrated platform for genomic, pharmacogenomic, and immunogenomic gene set cancer analysis. This common database integrates over 10,000 multi-dimensional genomic data across 33 cancer types from TCGA. We evaluated the correlation among mutation, methylation and mRNA expressions in GSCA database. Additionally, we also determined the correlation between prognosis and mutation or methylation.

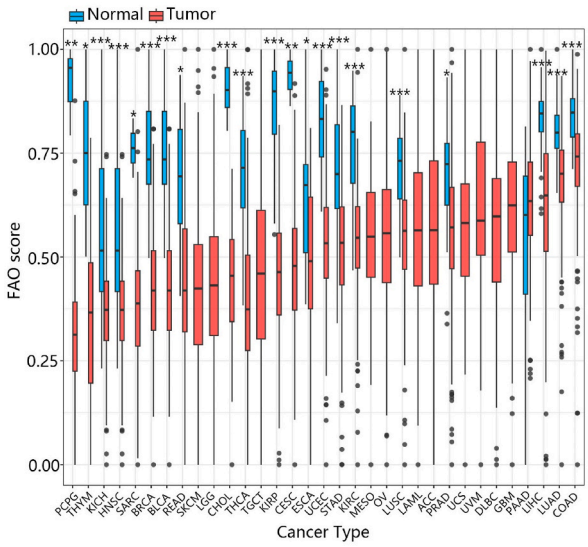

Fig. 1. FAO scores in 33 cancer types based on the TCGA database.

2.11. Drug sensitivity analysis in pan-cancer

As a comprehensive platform, GSCA also collected over 750 small molecule drugs from GDSC and CTRP. In a nutshell, based on the drug sensitivity data of GDSC and CTRP on the GSCALite website, we analyzed the relationship between some drugs and 15 FAO genes.

2.12. Statistical analysis

In this study, all data were analyzed in R software (version 4.2.2). The independent sample *t*-test was used to calculate the difference between the two groups. The survival difference was evaluated by cox regression analysis followed by the log-rank test. The correlation analysis was identified by the Pearson test. $p < 0.05$ was considered a significant difference.

3. Results

3.1. The landscape of FAO scores in 33 cancer types

We ranked the 33 cancer types according to their FAO scores and TCGA database (Fig. 1). It was obvious that the FAO score of colon adenocarcinoma (COAD) was highest among all cancer types, while PCPG was lowest. Additionally, the FAO scores were significantly decreased in tumor samples compared with normal samples except for PAAD.

3.2. The univariate cox analysis of FAO scores

Furthermore, we used TCGA clinical data to examine the prognostic value of FAO scores in 33 cancer types. All the statistical data

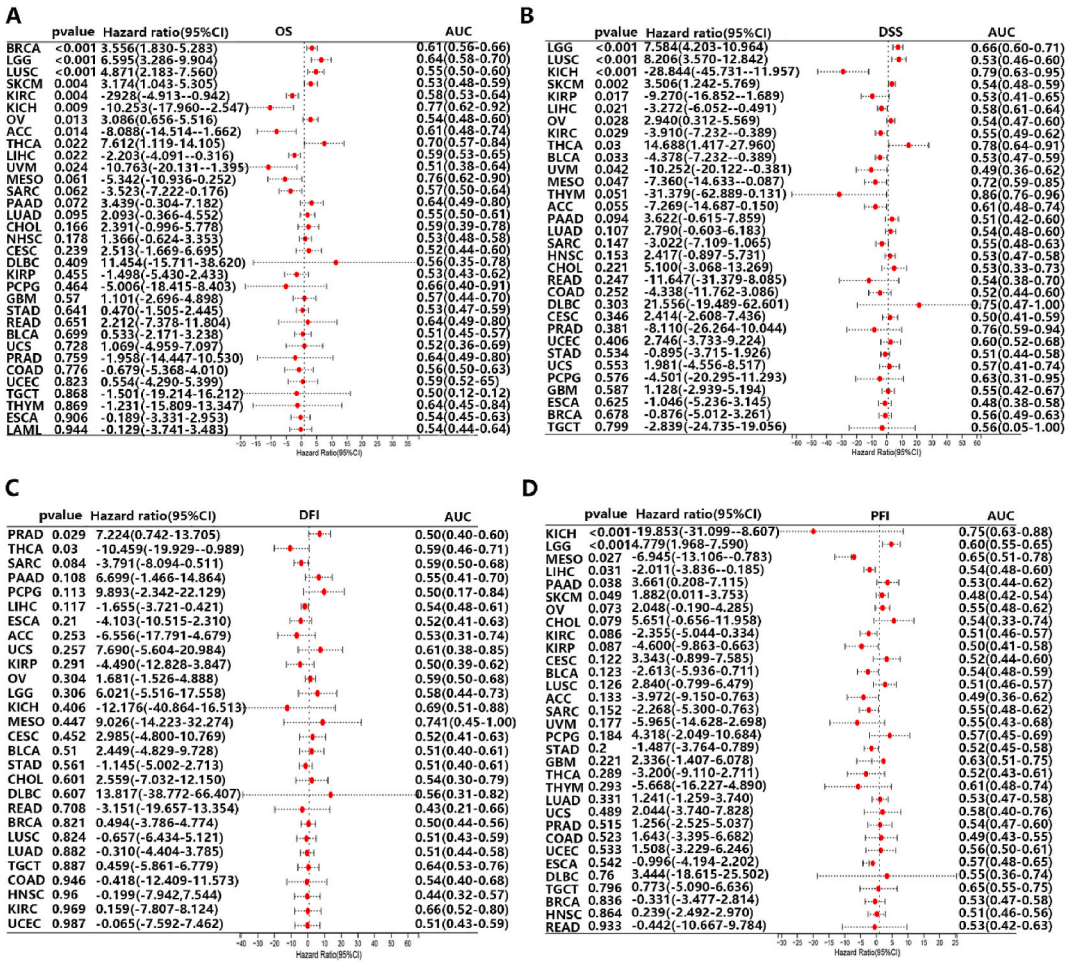

Fig. 2. Relationship between FAO scores and clinical outcomes of patients in pan-cancer. (A) Univariate Cox regression analysis of (A) OS, (B) DSS, (C) DFI and (D) PFI.

was displayed in Fig. 2. Higher FAO score was significantly associated with a poorer OS in breast invasive carcinoma (BRCA), brain lower grade glioma (LGG), lung squamous cell carcinoma (LUSC), skin cutaneous melanoma (SKCM), ovarian cancer (OV), and thyroid carcinoma (THCA) (Fig. 2A). On the contrary, increased FAO score was related to the better prognosis in kidney renal clear cell carcinoma (KIRC), kidney chromophobe (KICH), adrenocortical carcinoma (ACC), liver hepatocellular carcinoma (LIHC), and uveal melanoma (UVM). Disease free survival (DSS) was also calculated. Compared with OS, the results were much similar (Fig. 2B). Elevated oxidation score was significantly associated with a poorer DSS in brain lower grade glioma (LGG), LUSC, SKCM, OV, and THCA. In contrast, a low oxidation score was related to a poorer DSS in KIRC, KICH, kidney renal papillary cell carcinoma (KIRP), LIHC, bladder urothelial carcinoma (BLCA), UVM, and mesothelioma (MESO). Moreover, we analyzed disease free internal (DFI) and progress free internal (PFI) to get more prognostic information. In DFI, a high FAO score was probably an adverse factor for prostate adenocarcinoma (PRAD), however, that was possibly a protective factor for THCA (Fig. 2C). In PFI, a high FAO score could be a negative factor for LGG, pancreatic adenocarcinoma (PAAD), and SKCM. Conversely, a high FAO score could be a positive factor for LICH, mesothelioma (MESO), and LIHC (Fig. 2D). These results clearly demonstrated that the FAO score was significantly associated with patient outcomes in multiple cancer types.

3.3. The function analysis of FAO scores using GSVA

To explore the biological significance of FAO scores in the different tumors, we calculated the scores of signal pathways using GSVA and assessed the relationship between oxidation scores and GSVA scores. As shown in Fig. 3, FAO scores were positively and negatively related to some signal pathways related to immune response, such as TGF beta signaling and TNFA signaling via NFKB.

3.4. The role of FAO in immune infiltration and immune therapy

As we observed the distinct relationship between FAO scores and the immune response, we first assessed the association between FAO scores and tumor microenvironment (TME) in pan-cancer. The results indicated that there was a significant correlation between FAO scores and TME-relate scores (Fig. 4A). The correlation between tumor purity and FAO scores was opposite to the correlation between ESTIMATE scores and FAO scores. What's more, we found that the Stromal score, immune score and ESTIMATE score were all significantly and positively related to the FAO scores in OV, LAML and LGG.

Then, we further exhibited the landscape of FAO scores correlating with various immune cell infiltrations in different cancers. As shown in Fig. 4B, the FAO scores of testicular germ cell tumors (TGCT) and OV were positively correlated with the immune infiltrating levels of cancer-associated fibroblasts (CAFs). Besides, we confirmed the relationship between FAO score and immunosuppressive genes, chemokines, and chemokine receptors (Fig. 5A–C). The profile indicated that the FAO score was positively correlated with immunosuppressive genes, chemokines, and chemokine receptors in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), OV, and LGG. But the FAO score in UVM, THCA, and KIRC was negatively associated with immune-related genes.

Fig. 3. The correlation between GSVA scores of hallmark pathways and FAO scores in pan-cancer. Red indicates positive correlations while blue indicates negative. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

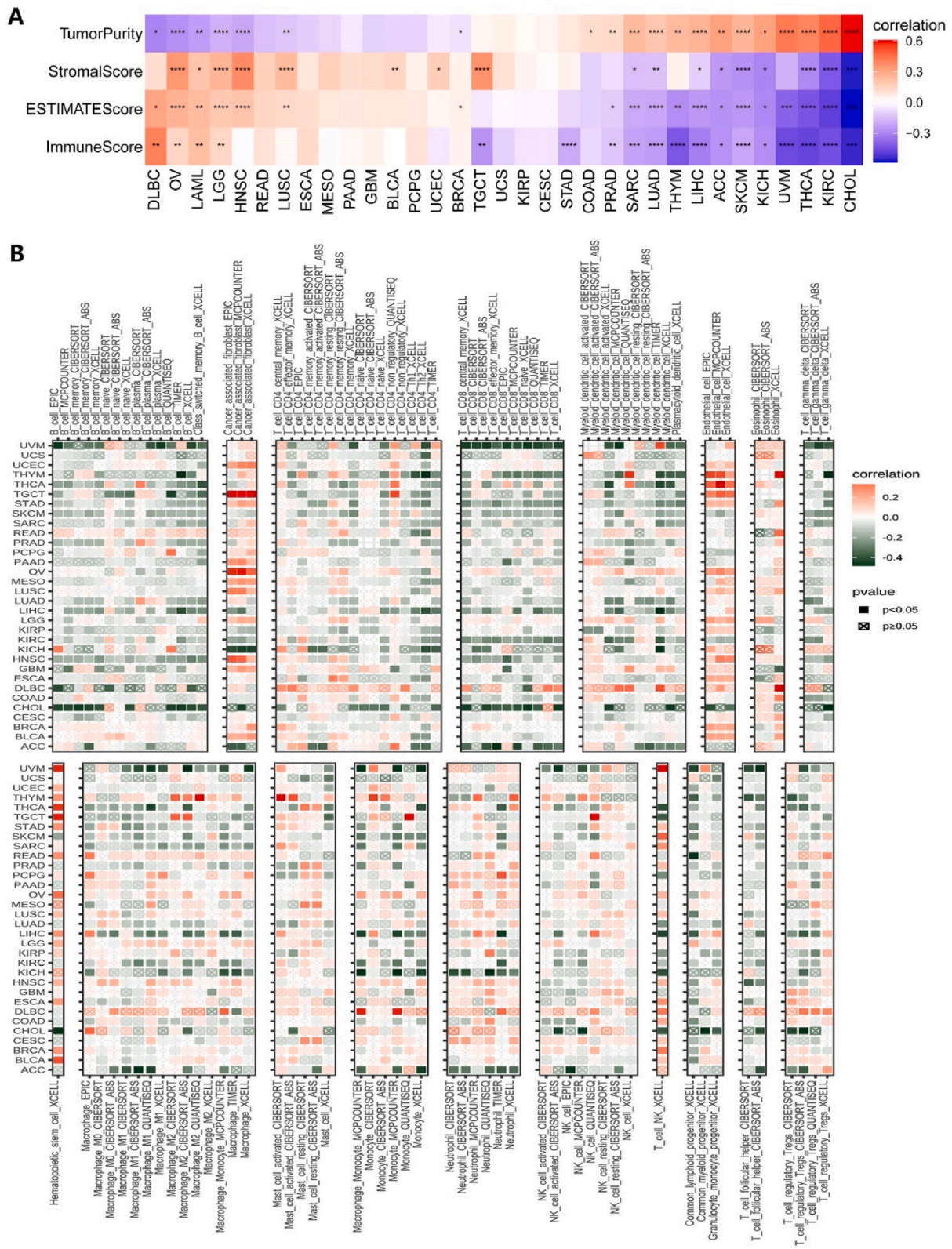

Fig. 4. The immune infiltration analysis of FAO scores in pan-cancer. (A) The relation between FAO scores and TME-related scores including tumor purity, stromal score, ESTIMATE score, and immune score. (B) The relation between FAO scores and immune cells.

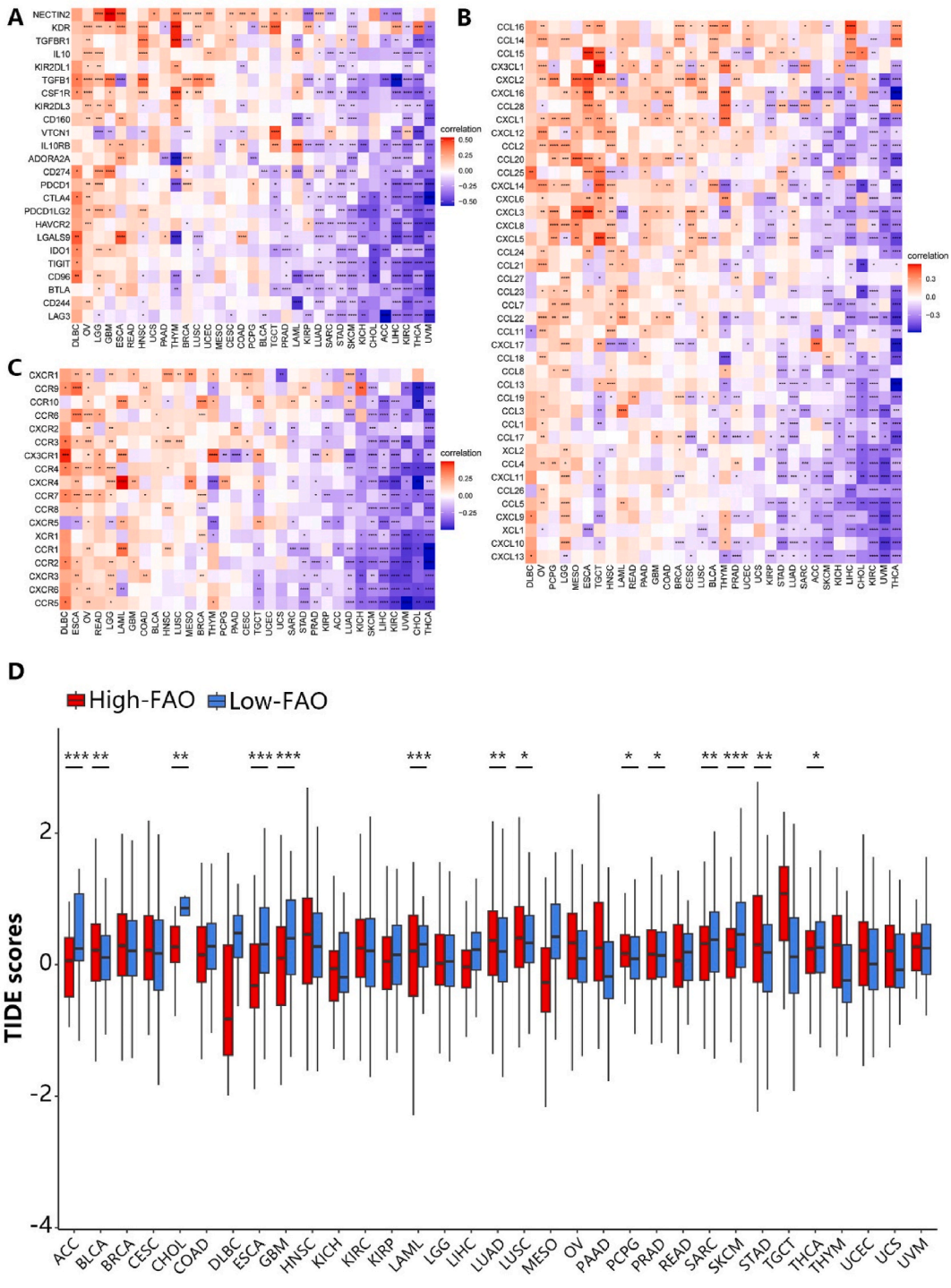

Fig. 5. FAO scores were closely related to immune-related genes and immune therapy. (A–C) The correlation between FAO scores and (A) immunosuppressive genes. (B) Chemokines. (C) Chemokine receptors. (D) The TIDE scores in high-FAO group and low-FAO group. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

As described by previous studies, the results of immunotherapy were affected by the level of immune infiltration [14]. Therefore, we further assessed the prognosis value of FAO in immune therapy. As presented in Fig. 5D, it was found that the TIDE scores were significantly increased in low FAO score group of ACC, CHOL, ESCA, GBM, LAML, SARC, SKCM and THCA, and FAO score was negatively related to the TIDE scores in these cancers expect GBM and THCA (Table 1). On the other hand, TIDE score was significantly

Table 1
The correlation between FAO score and TIDE score.

Cancer	correlation	pvalue
ACC	−0.389	<0.001
CHOL	−0.779	<0.001
ESCA	−0.291	<0.001
GBM	−0.022	0.771
LAML	−0.164	0.045
SARC	−0.188	0.002
SKCM	−0.188	<0.001
THCA	−0.53	0.203
BLCA	0.14	0.004
LUAD	0.033	0.423
LUSC	0.14	0.001
PCPG	0.141	0.045
PRAD	0.042	0.327
STAD	0.15	0.002

decreased in low FAO score group of BLCA, LUAD, LUSC, PCPG, PRAD and STAD, and FAO score was positively related to the TIDE scores in these cancers expect LUAD and PRAD. It indicated that the patients with high FAO score could benefit from immunotherapy in ACC, CHOL, ESCA, LAML, SARC and SKCM, and the patients with low FAO score could benefit from immunotherapy in BLCA, LUSC, PCPG and STAD.

3.5. The relationship between the FAO genes in pan-cancer

In addition, we analyzed the regulation of FAO-gene expressions in different cancer types. Because the normal samples of some tumors were lacked in TCGA and GTEx databases, we evaluated the change of these genes in 30 cancers compared with that of corresponding normal samples except for MESO, SARC and UVM. From Fig. 6, it could be seen that all FAO genes were significantly up- or down-regulated in BRCA, ESCA, KIRP, OV, SKCM, THYM and UCEC. Therefore, we further validated the expression of these genes using IHC. The results identified that ABCD1 and PPARD were significantly upregulated in BRCA samples, while ABCD2, IRS2, MLYCD and PLIN5 were significantly downregulated (Fig. 7A–D). Besides, ABCD1, IRS2, PLIN5, PPARD and PPARGC1A were significantly upregulated in OV samples, while ABCD2, AKT2, CPT1A, FABP1IRS1, MLYCD, NR4A3 and TWIST1 were downregulated (Fig. 8A–D).

3.6. The expression of FAO genes in pan-cancer based on the scRNA data

In our study, we utilized single-cell RNA analysis (scRNA) to investigate the expression patterns of FAO genes in different cell types (Supplement Fig 1–15). Our results revealed distinct expression profiles. Specifically, ABCD1, IRS2, NR4A3, and PPARD exhibited predominant expression in monocytes and macrophages in glioma. ABCD2 showed high expression in astrocyte-like malignant cells and CD8 T cell exhaustion (Tex). AKT2, CPT1A, and MTLN were highly expressed in astrocyte (AC)-like malignant cells in glioma. FABP1 displayed elevated expression in epithelial cells in colorectal cancer (CRC). IRS1 and MLYCD exhibited high expression in oligodendrocyte progenitor cell (OPC)-like cells in glioma. Plin5 demonstrated high expression in astrocytes in glioma. PPARA displayed elevated expression in oligodendrocytes in glioma. PPARGC1A showed high expression in endothelial cells in hepatoblastoma (HB). Lastly, TWIST1 was highly expressed in fibroblasts in breast cancer (BRCA). Overall, our findings indicate that most FAO genes

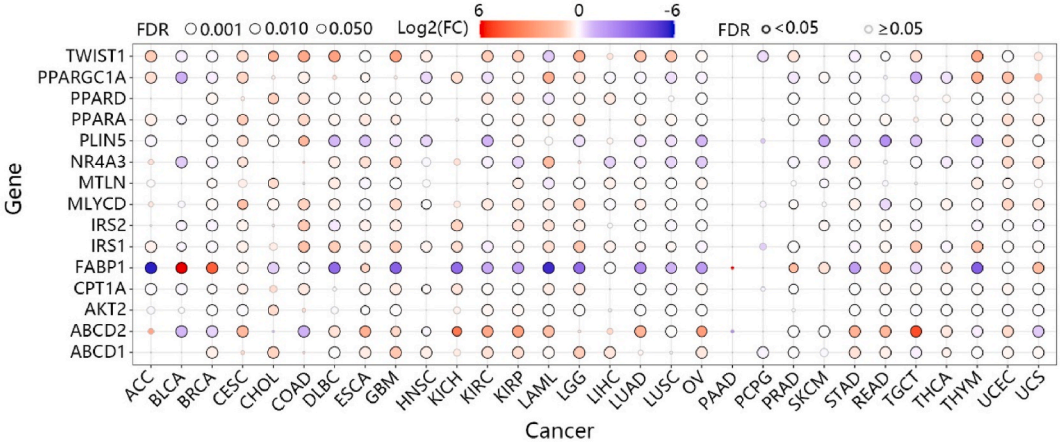

Fig. 6. The expression of 15 FAO genes in 30 cancers compared to the normal samples.

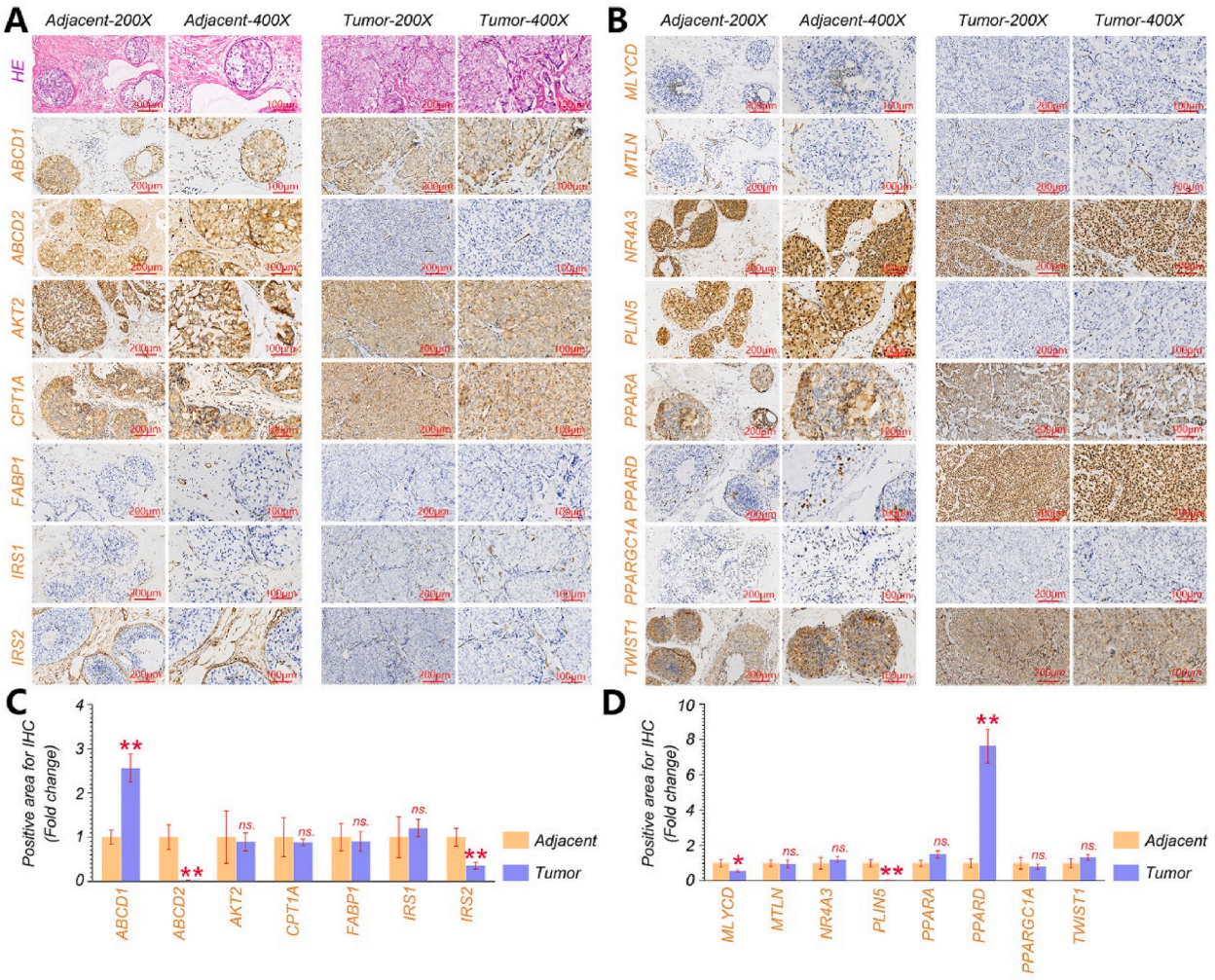

Fig. 7. The IHC analysis of the 15 FAO genes in BRCA samples. (A–B) The protein expressions of FAO genes in normal and BRCA samples using IHC. (C–D) The quantification of FAO gene protein expressions in normal and BRCA samples.

are predominantly and highly expressed in monocytes, macrophages, and astrocyte-like malignant cells in glioma.

3.7. Copy number variation (CNV) and methylation of FAO genes

Then, we tried to explore the factors which could affect the mRNA expression of FAO genes and prognosis. CNV was an important molecular mechanism in cancers. Fig. 9A displayed that the CNV of FAO genes was positively related to the mRNA expression in pan-cancer. Fig. 9B indicated CNV of FAO genes mainly played a positive role in UCEC and KIRP in DFI. But it was positively related to more cancer types in DSS, OS and PFI (Fig. 9C–E).

Next, we explored whether DNA methylation is a regulatory factor of FAO genes. As shown in Fig. 10A, most of the mRNA expressions of FAO genes were negatively associated with methylation in pan-cancer. However, most methylation of FAO genes was not significantly related to the OS, DSS, DFS and PFI (Fig. 10B–E).

3.8. The correlation between drug sensitivity and expression of FAO genes

Finally, we explored the potential predictive value of FAO genes in targeted therapy. We analyzed the correlation between the mRNA expression of FAO genes and the drug response based on the GDSC and CTRP databases (Fig. 11A–B). The results implied a strong negative correlation between the mRNA expression of NR4A3, IRS2, and ABCD1 and the sensitivity of most drugs in GDSC. In CTRP, the drugs, such as indisulam and Compound 7d-cis were positively correlated with PPARD and IRS1 but had a negative correlation with AKT2 and ABCD2.

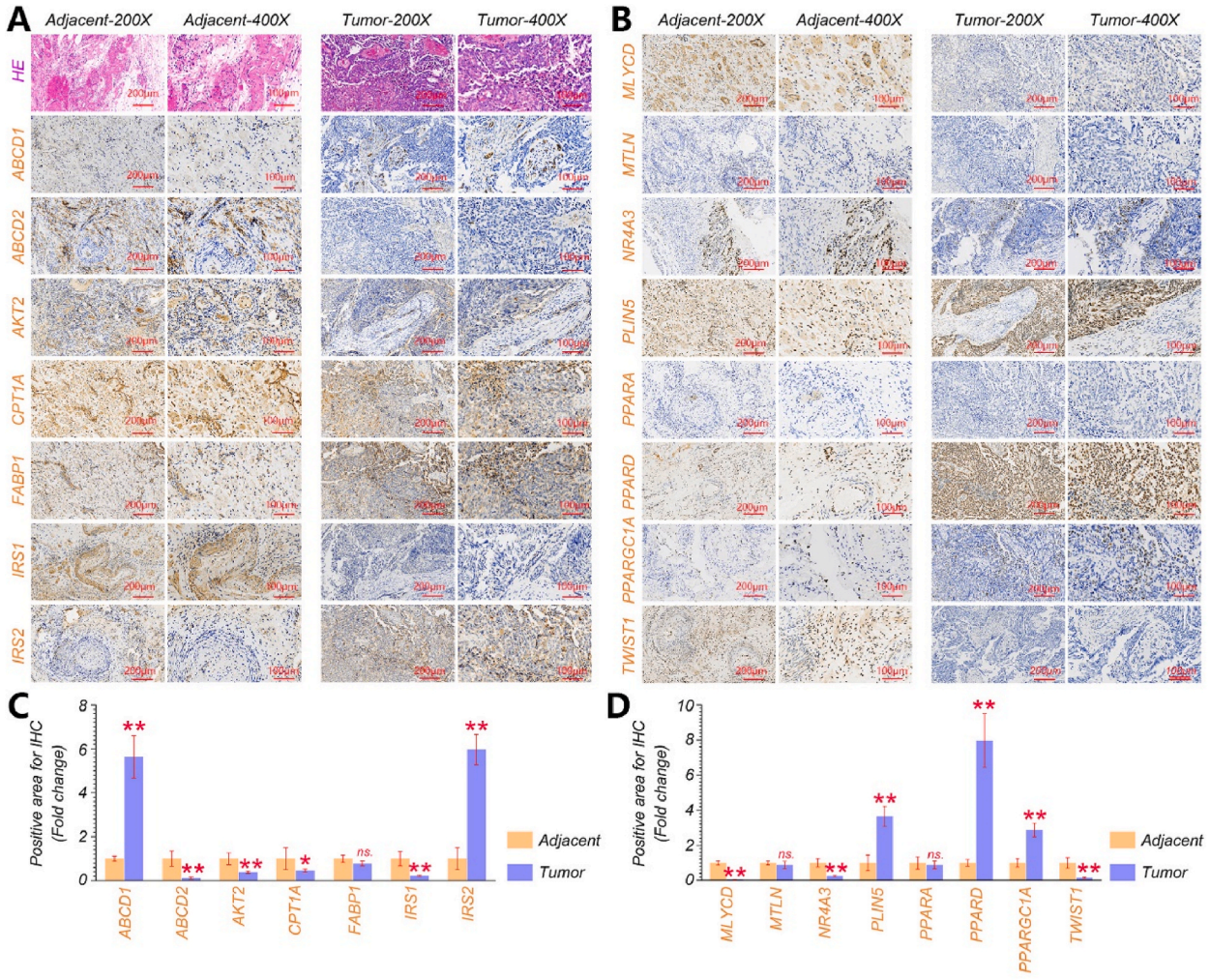

Fig. 8. The IHC analysis of the 15 FAO genes in OV samples. (A–B) The protein expressions of FAO genes in normal and BRCA samples using IHC. (C–D) The quantification of FAO gene protein expressions in normal and BRCA samples.

4. Discussion

FAO plays a crucial role in cancer cells and is necessary for cell proliferation, survival, stemness, drug resistance and metastasis [5, 15]. Guo et al. identified that the suppression of FAO caused the accumulation of lipids and promoted the development of HCC cells [16]. However, Crunkhorn et al. also determined that the suppression of FAO progress inhibited the development of TNBC [17]. These results suggested that FAO had a dual impact on the development of different cancer cells except for the production of ATP. According to previous studies, it had been proven that FAO was involved in the promotion of tumor development through multiple pathways. For example, Wang et al. identified that the FAO positively affected angiogenesis [18]. On the other hand, FAO was involved in the immune response. In vitro experiments, it has been proven that the inhibition of FAO led to the increasing death rate of memory CD8 T cells [19]. Besides, FAO was essential for the migration of tumor cells mediated by M2 macrophages through upregulating the IL-1β expression [20]. In this study, we first comprehensively calculated and ranked FAO scores in 33 cancer datasets obtained from TCGA, and we found it was highest in COAD and lowest in PCPG. Consistent with previous studies, we found the positive or negative role of FAO scores depended on the cancer types in the OS, DSS, DFI and PFI based on the univariate Cox regression analysis. Additionally, the GSVA analysis showed that FAO was associated with immune-related signal pathways in pan-cancer, which suggested that FAO may play a role in the immune progress through regulating signal pathways.

Tumor microenvironment (TME), as a research hotspot, could affect tumor progression and recurrence [21]. Immune cells in TME had been reported to harbor tumor-promoting as well as tumor-suppressing activities. They were considered as a significant determining factor of the response to immunotherapy and clinical outcome. Our study showed that FAO score was significantly related to TME in various cancer types, and FAO might be significantly positively correlated with the infiltration of CAFs which was the major generators of tumor extracellular matrix (ECM) components in many cancers [22]. Additionally, CAFs could result in an

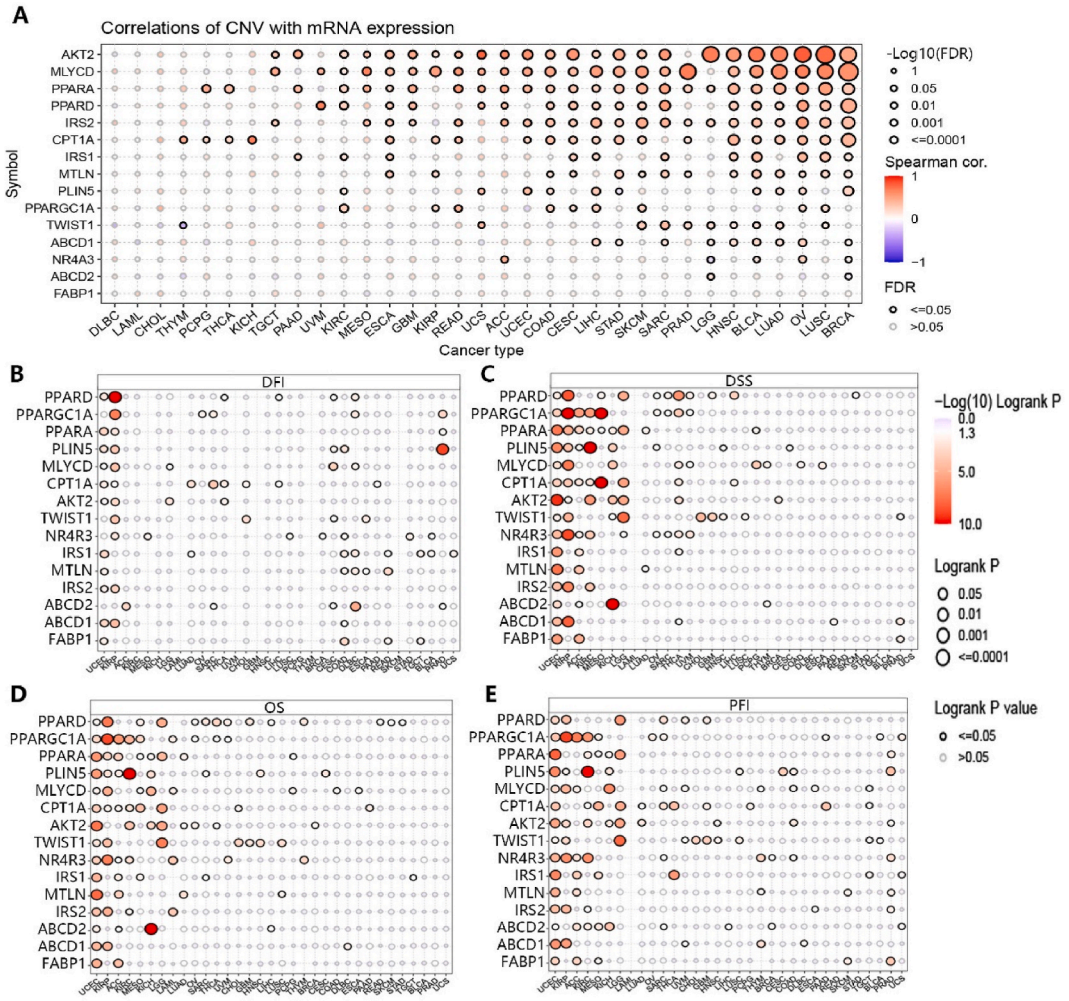

Fig. 9. The effect of CNV on the expression of FAO genes and prognosis in pan-cancer. (A) The correlation between CNV and mRNA expressions of FAO genes. (B–E) The correlation between CNV and prognosis in (B) DFI, (C) DSS, (D) OS and (E) PFI.

immunosuppressive TME and secrete various chemokines and cytokines to promote cancer invasion and metastasis [23]. The further analysis identified that FAO was mainly and positively related to the immune response in OV, LAML and LGG. Moreover, we also found that most immune-related genes were positively and significantly related to the FAO in many cancers, especially DLBC and OV, while it was negatively related to some cancer types including THCA, KIRC and KICH. Furthermore, immune infiltration was essential for the successful results of immune therapy [24]. Besides, higher TIDE score is associated with poor immune checkpoint suppression therapy [25]. Gao et al. found that FAO has the potential to generate reactive oxygen species (ROS), which can induce immunogenic cell death (ICD). This process enhances the anti-tumor efficacy of PD-L1 silencing [26]. Wu et al. identified that increasing FAO inhibited the production of IL-22 and attenuates the activation of lymphoid tissue inducer (LTi) cells, and LTi cells were found to express high levels of PD-1 [27]. It suggested that FAO could affect the efficiency of anti-PD-1 immunotherapy. However, a scRNA analysis identified that FAO was activated in tumor and T cells, which caused the tumor metastasis and depletion of immune cells [28]. Besides, clinical studies have shown that FAO inhibitors could improve the effect of chemotherapy or immunotherapy [29]. These results indicated that FAO has two sides for immunotherapy. Similarly, we found that FAO was positively relate to the TIDE score in some cancers, while it was negatively related to other cancers. Moreover, the TIDE results indicated that the effect of immunotherapy is better for patients with high FAO scores and diagnosed with BLCA, LUAD, LUSC, PCPG, PRAD and STAD because of the poor immune escape ability of tumor cells. It suggested that the immune therapy was suitable for the patients with high FAO scores and diagnosed with one of these cancers.

As we all know, a host of biological progress including the development of tumors was derived by mRNA expression. Moreover, the mRNA expression could be regulated by DNA methylation, which was a main kind of epigenetic modification of DNA, and DNA mutation [30,31]. Thus, we explored the role of 15 FAO genes in pan-cancer. We found that most FAO genes were downregulated in pan-cancer. However, the IHC results found that the protein expression levels of some genes were not consistent with mRNA expressions based on bioinformatics analyzed. It may be because the number of experimental samples is too small and individual

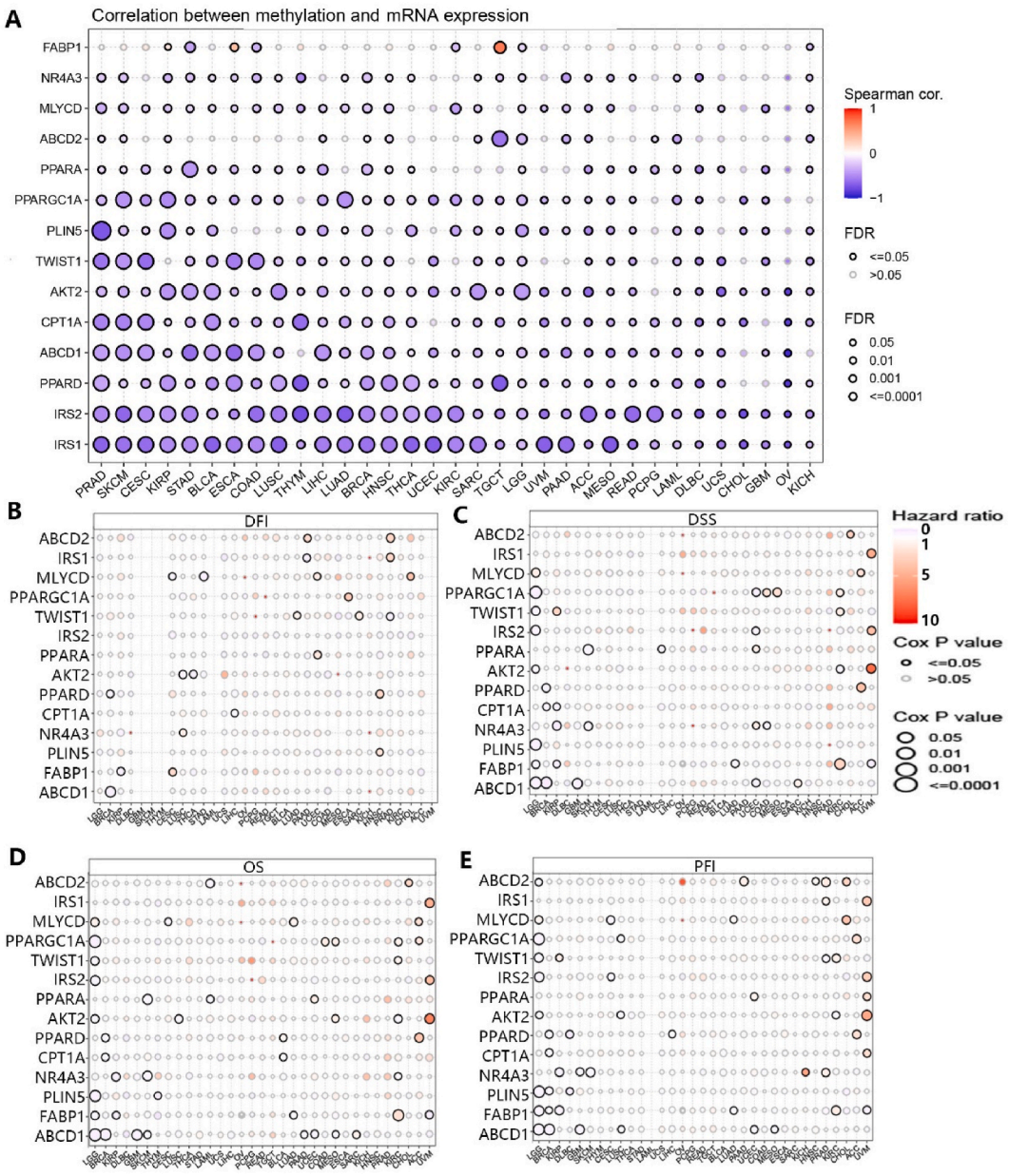

Fig. 10. The effect of methylation on the expression of FAO genes and prognosis in pan-cancer. (A) The correlation between methylation and mRNA expressions of FAO genes. (B–E) The correlation between methylation and prognosis in (B) DFI, (C) DSS, (D) OS and (E) PFI.

differences are not excluded. Additionally, the K-M curve showed higher expressions of most FAO genes were associated with poorer prognosis except for MTLN, FABP1 and ABCD2. It indicated that activation of the FAO pathway may inhibit cancer cell proliferation, and improve outcomes of patients with some cancers. In addition, we found that CNV and methylation were positively and negatively related to most FAO genes in cancers, respectively. Furthermore, there was a positive relation between the CNV of most FAO genes and prognosis in UCEC and KIRC. However, methylation of some FAO genes was negatively related to the prognosis in a few cancer types. These results indicated that the mutation of FAO genes had a more vital function in the prognosis of cancers than methylation. In consideration of the meaning of therapy in cancer treatment, we also assessed the correlations of FAO genes and small-molecule compounds in cancers. The results revealed that FAO genes could be a target of immune therapy for some cancers.

In a word, our results suggested that FAO was involved in tumorigenesis, development, and treatment. We believe that FAO could be used as an important therapeutic target and valuable prognosis factor concerning cancers in the future. However, the data in this study was retrospective from a common database. Further experimental and clinical trials should be performed to confirm the function of FAO in tumors.

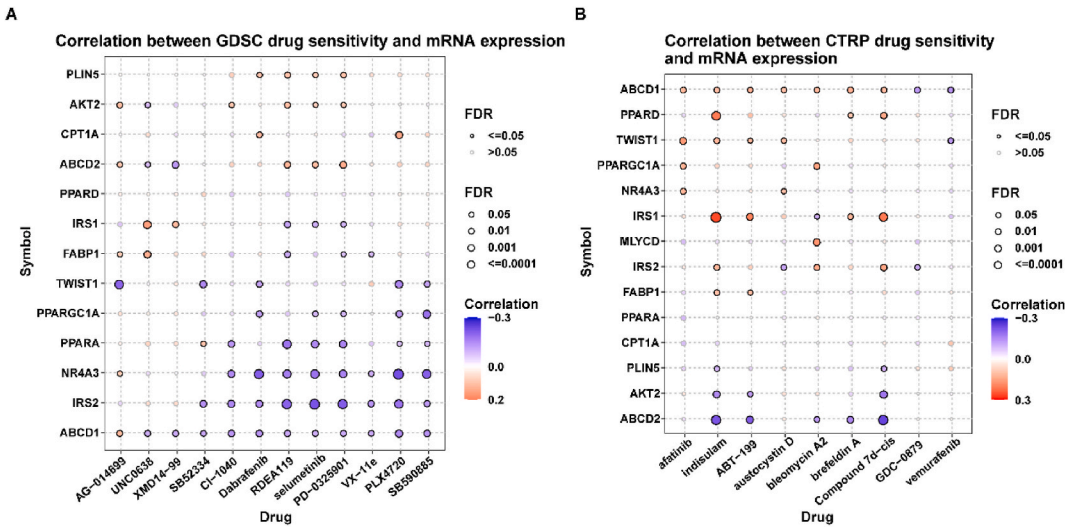

Fig. 11. The predictive value of FAO score in targeted therapy. (A) The correlation between gene expression and the sensitivity of GDSC drugs in pan-cancer. (B) The correlation between gene expression and the sensitivity of CTRP drugs in pan-cancer.

Data availability

Data will be made available on request.

Consent for publication

Not applicable.

Ethical approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Ningbo University. Ethics Approval Number: NBU-2023-085. All patients who were familiar with the contents and processes of the study and able to complete all the scheduled study processes signed the informed consent. Our study complies with the Declaration of Helsinki.

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CRediT authorship contribution statement

Fu-bin Zhang: Writing – original draft, Validation, Funding acquisition, Data curation, Conceptualization. **Lei Gan:** Writing – original draft, Formal analysis, Data curation. **Tian-hong Zhu:** Writing – original draft, Methodology, Formal analysis, Data curation. **Hui-qing Ding:** Writing – original draft, Methodology, Formal analysis. **Cheng-hao Wu:** Writing – original draft, Methodology. **Yu-tao Guan:** Writing – original draft, Formal analysis, Conceptualization. **Xue-qin Chen:** Writing – original draft, Funding acquisition, Data curation, Conceptualization.

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.

Acknowledgment

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28441.

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