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Pan-cancer and single-cell analysis reveal THRAP3 as a prognostic and immunological biomarker for multiple cancer types

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Background: Thyroid hormone receptor-associated protein 3 (THRAP3) is of great significance in DNA damage response, pre-mRNA processing, and nuclear export. However, the biological activities of THRAP3 in pan-cancer remain unexplored. We aimed to conduct a comprehensive analysis of THRAP3 and validate its expression levels in lung cancer.

Methods: A pan-cancer analysis was conducted to study the correlation of THRAP3 expression with clinical outcome and the tumor microenvironment based on the available bioinformatics databases. The protein levels of THRAP3 were explored in lung cancer by immunohistochemistry (IHC) analysis. Single-cell sequencing (ScRNA-seq) analysis was employed to investigate the proportions of each cell type in lung adenocarcinoma (LUAD) and adjacent normal tissues, along with the expression levels of THRAP3 within each cell type.

Results: THRAP3 is upregulated in multiple cancer types but exhibits low expression in lung squamous cell carcinoma (LUSC). Immunohistochemistry results showed that THRAP3 is a lowly expression in LUAD and LUSC. THRAP3 elevation had a poor prognosis in kidney renal clear cell carcinoma and a prolonged survival time in kidney chromophobe, brain lower-grade glioma and skin cutaneous melanoma, as indicated by the KM curve. Single-cell analysis confirmed that the proportions of T/B cells, macrophages, and fibroblasts were significantly elevated in LUAD tissues, and THRAP3 is specifically overexpressed in mast cells.

Conclusion: Our findings uncover that THRAP3 is a promising prognostic biomarker and immunotherapeutic target in multiple cancers, but in LUAD and LUSC, it may be a protective gene.

KEYWORDS

biomarker, pan-cancer, immune infiltration, prognosis, single cell

Introduction

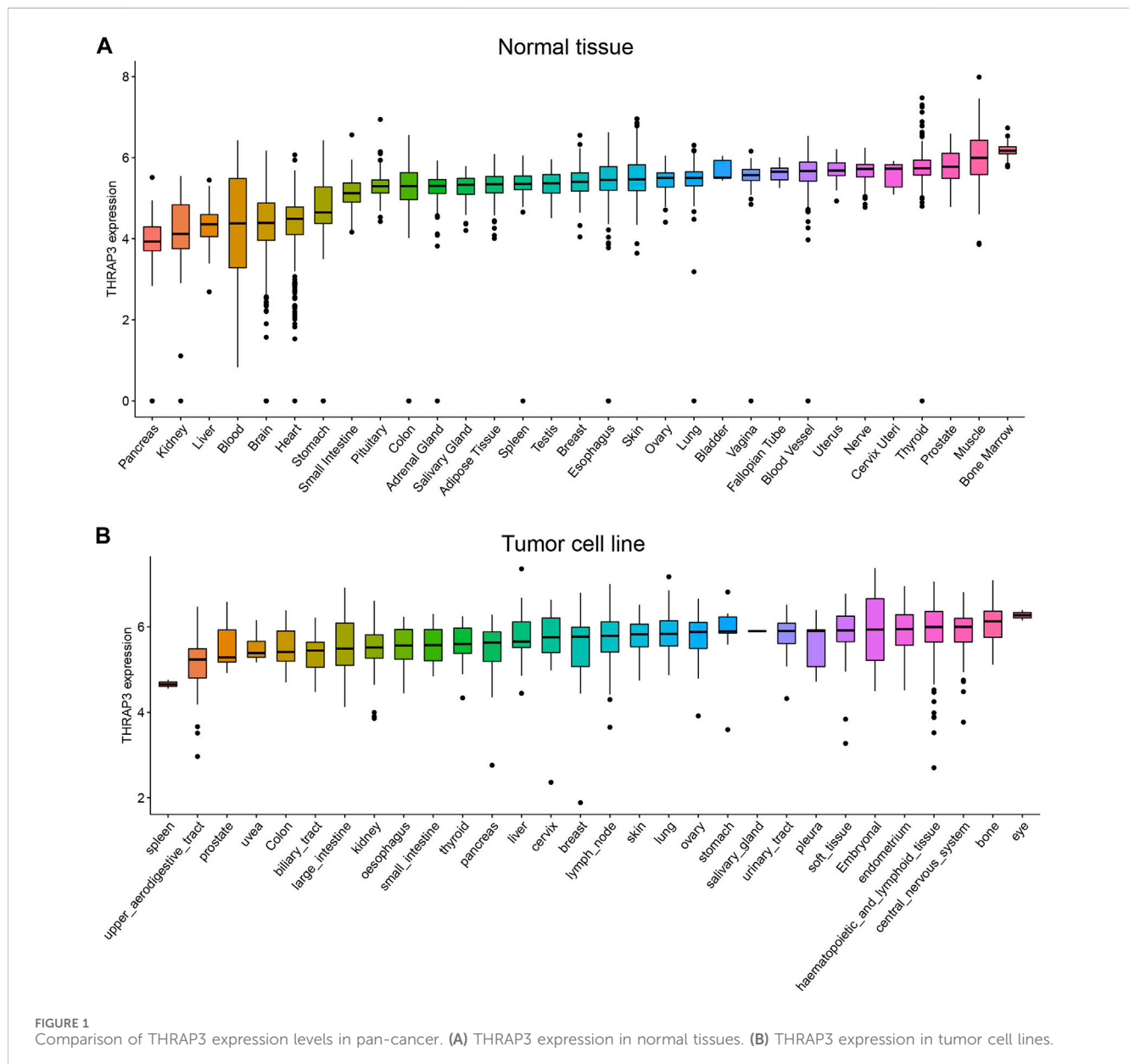
Cancer poses a grave risk to human life and health, and lung cancer has the greatest fatality rate (Thai et al., 2021; Ma et al., 2022a; Ma et al., 2022b; Siegel et al., 2023). There is currently no effective treatment for cancer. Recent research indicates that immunotherapy, as exemplified by immune checkpoint inhibitors, has demonstrated more significant potential in treating lung cancer and other cancers (Doroshov et al., 2021; Passaro et al., 2022; Ma et al., 2023a; Ma et al., 2023b). Therefore, we aimed to identify possible biomarkers and therapeutic targets for tumors by conducting comprehensive analysis, based on the Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) datasets.

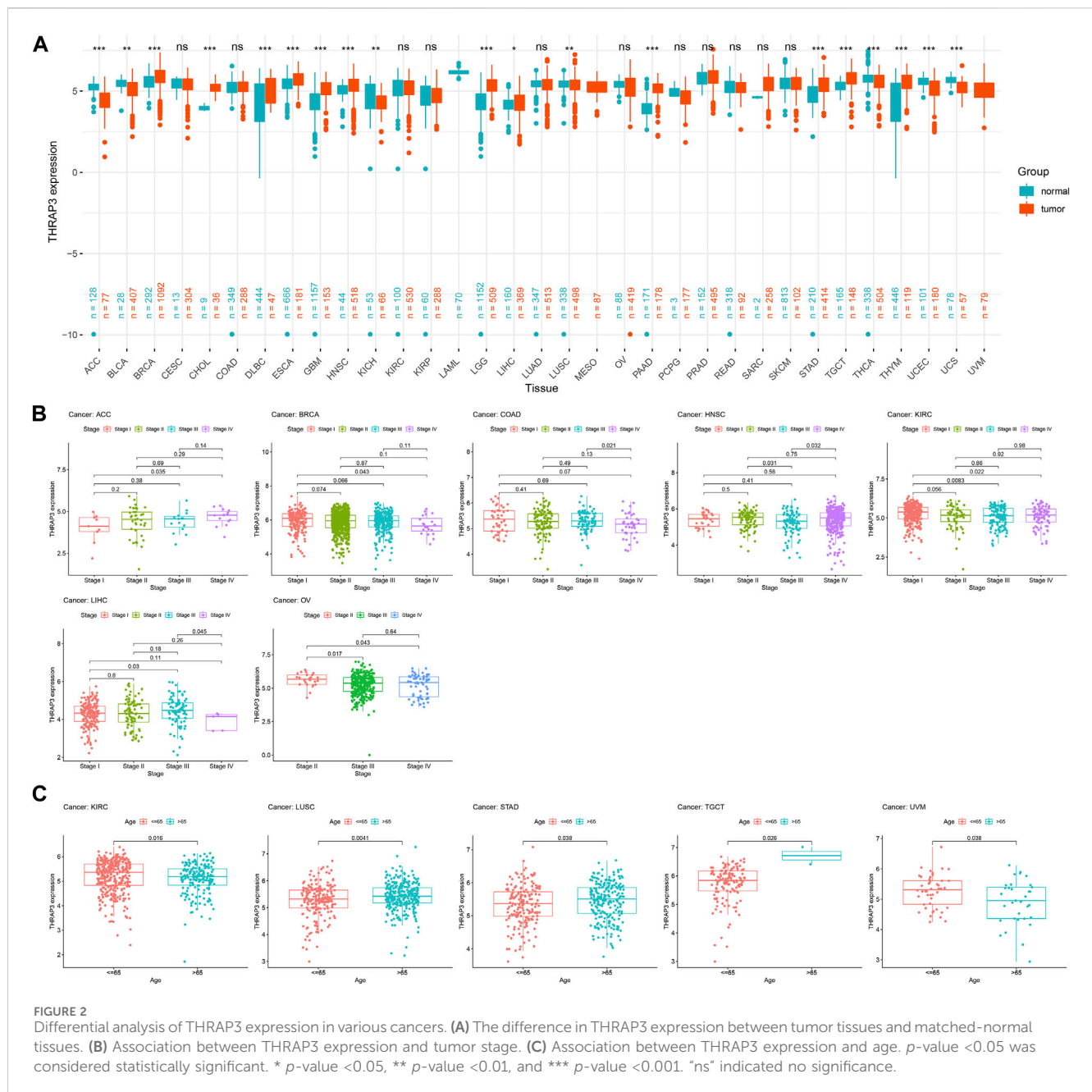
THRAP3 is a nuclear receptor coactivation factor that interacts with multiple nuclear receptors in a ligand-dependent manner. THRAP3 is structurally located in chromosome 1p34. This transcript encoded 955 amino acids with molecular masses of 150 kDa. Functionally, THRAP3 is involved in nuclear export,

DNA damage repair, and the maintenance of genomic stability (Beli et al., 2012; Voh et al., 2017).

The study by Li et al. found that THRAP3 is significantly correlated with the infiltration levels of immune cells and immune-related genes in kidney renal clear cell carcinoma (KIRC) (Li et al., 2022). THRAP3 was reported to be a tumor suppressor in BRAF-mutated colorectal cancer (Ma et al., 2022c). Mechanistically, nuclear PD-L1 interacts with THRAP3 to increase BUB1 expression, leading to cell proliferation. In cancer cells, THRAP3 facilitates cell growth by inducing R-loop resolution (Kang et al., 2021). In addition, phosphorylated THRAP3 is involved in tumor progression in the androgen-independent prostate (Ino et al., 2016).

Several studies have implicated THRAP3 in the development of certain cancers. However, there is no comprehensive analysis of the biological role of THRAP3 expression in pan-cancer. In order to investigate the expression level, prognostic significance, molecular





function, signaling pathways, and immune infiltration pattern of THRAP3 in 33 kinds of cancer, we conducted a systematic bioinformatics analysis and experimental validation in LUAD.

Methods

Data preprocessing and differential expression analysis

RNA-seq and clinical information for 33 cancers were downloaded from the TCGA database. On the UCSC Xena official website (<https://xenabrowser.net/datapages/>), we obtained the expression profiles of 1,076 tumor cell lines from the CCLC database and 7,862 normal tissues

from the Genotype-Tissue Expression (GTEx) database. All RNA-seq data were log₂ transformed.

The differential analysis of THRAP3 expression in pan-cancer was carried out based on R Studio (version 4.2.1). $p < 0.05$ was deemed significant.

Processing of scRNA-seq data

For our study, we chose the scRNA-seq dataset GSE149614 from the GEO database. The dataset contains single-cell RNA sequencing data from 2 LUAD tissues and 2 adjacent normal tissues. We employed the 'Seurat' R package to address batch effects among samples (Butler et al., 2018). Cells with a gene count between 100 and 7,500 and a

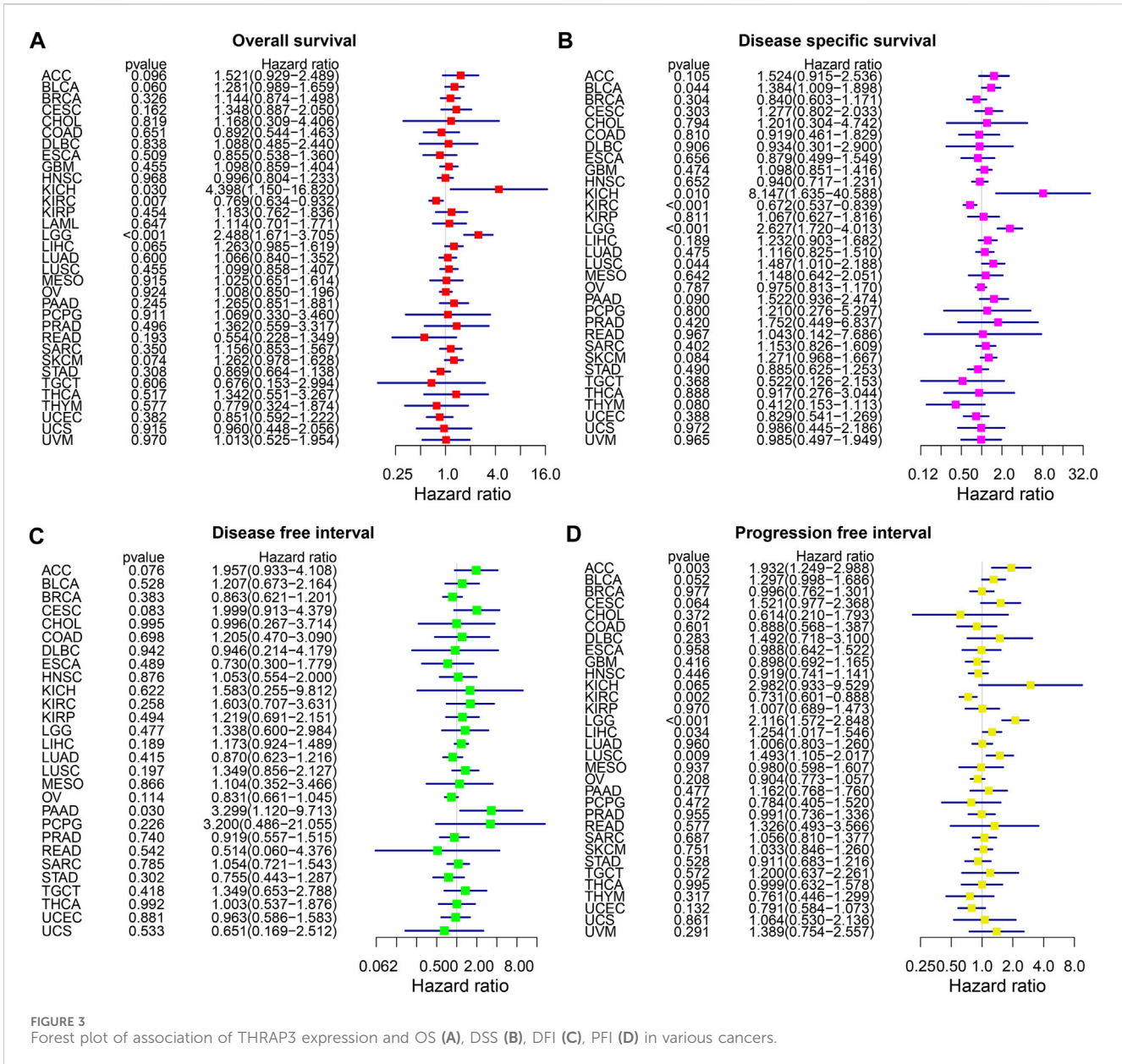


FIGURE 3 Forest plot of association of THRAP3 expression and OS (A), DSS (B), DFI (C), PFI (D) in various cancers.

mitochondrial gene proportion below 30% were included in the study, while cells deemed of low quality were excluded from the dataset. We standardized the data using the “Normalize Data” function and employed the “Find Variable Features” function to identify genes with specific expression patterns. The “RunPCA” function was applied for clustering and UMAP visualization dimension reduction on the dataset (Narayan et al., 2021). The “FindMarkers” function was used to analyze DEGs in various cell subtypes. We identified genes specific to each cell cluster and manually annotated cells using the Cellmarker (Hu et al., 2023) and PanglaoDB databases (Franzén et al., 2019). The “DotPlot” function from the “Seurat” package was utilized to create dot plots depicting the expression levels of THRAP3 across cell subtypes. The “FeaturePlot” function was employed to illustrate the expression distribution of each gene in the clustering plot.

Relationships between THRAP3 and prognosis

On the basis of TCGA data, the link between THRAP3 expression and pathological stage and age was investigated. Using the R packages “survival,” “survminer,” and “forestplot,” a Cox risk regression model was employed to investigate the relationship between THRAP3 expression and survival. To examine the role of THRAP3 in prognosis, the association between THRAP3 expression and over survival (OS), disease specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI) was studied (Ding et al., 2022; He et al., 2022; Wei et al., 2022). Utilizing the KM curve and the log-rank test, survival studies for each tumor were conducted.

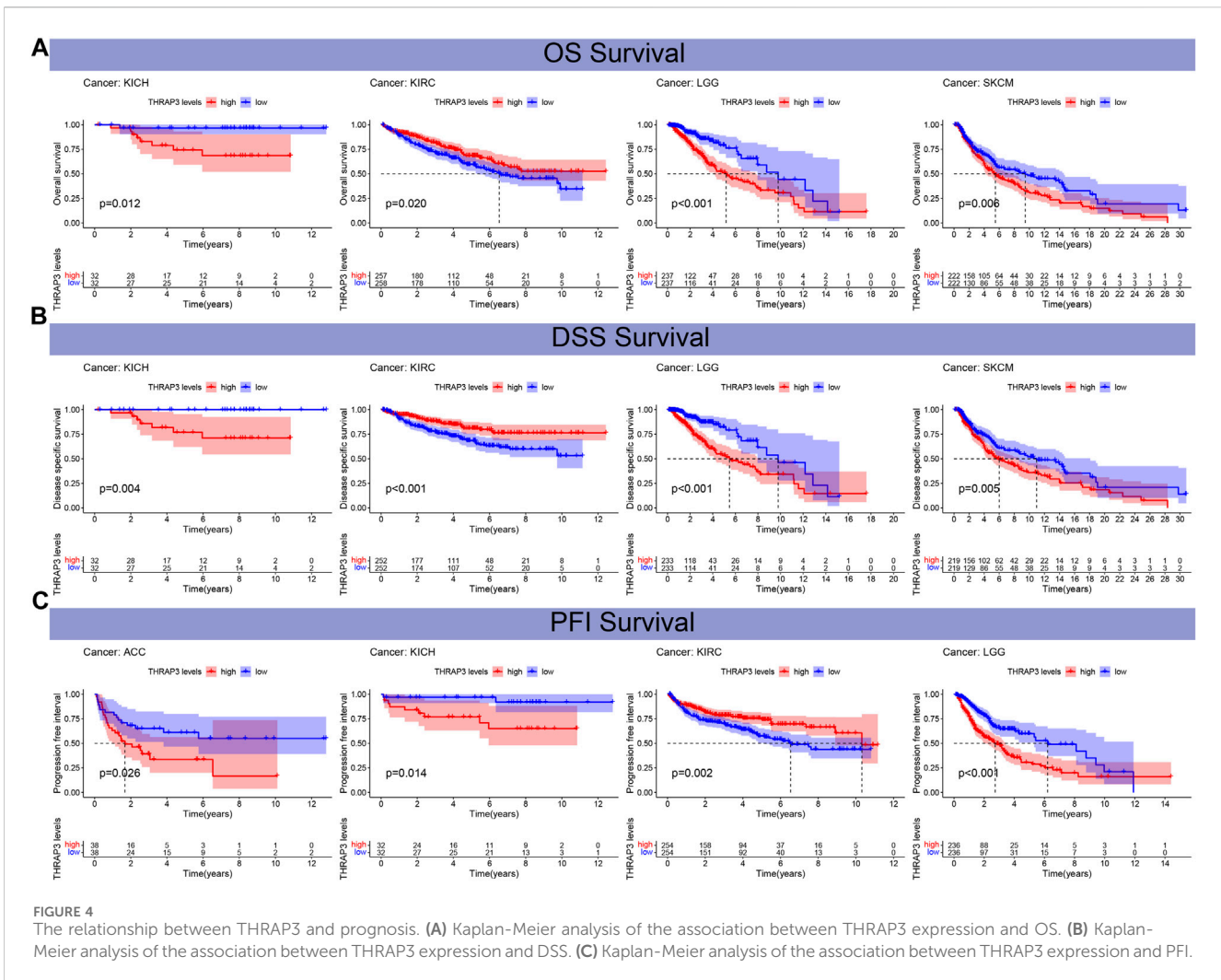


FIGURE 4 The relationship between THRAP3 and prognosis. (A) Kaplan-Meier analysis of the association between THRAP3 expression and OS. (B) Kaplan-Meier analysis of the association between THRAP3 expression and DSS. (C) Kaplan-Meier analysis of the association between THRAP3 expression and PFI.

IHC analysis

Human tissue microarrays of LUAD, and LUSC (R101Lu01; Wuhan Boster Biotechnology, Wuhan, China) were purchased. The clinical characteristics of 30 paired LUSC and LUAD specimens were obtained from the company’s websites. With an anti-THRAP3 (PU300969, 1:500) antibody, immunohistochemistry (IHC) was performed. The chips were scanned using a Leica APERIO VERSA 8 tissue Microarray Scanner. Imagescope software automatically identifies dark brown as strongly positive, brown yellow as moderately positive, light yellow as weakly positive, and blue nuclei as negative on tissue sections and analyzes its area (in pixels), the percentage of positives.

Relationship between THRAP3 expression and TME

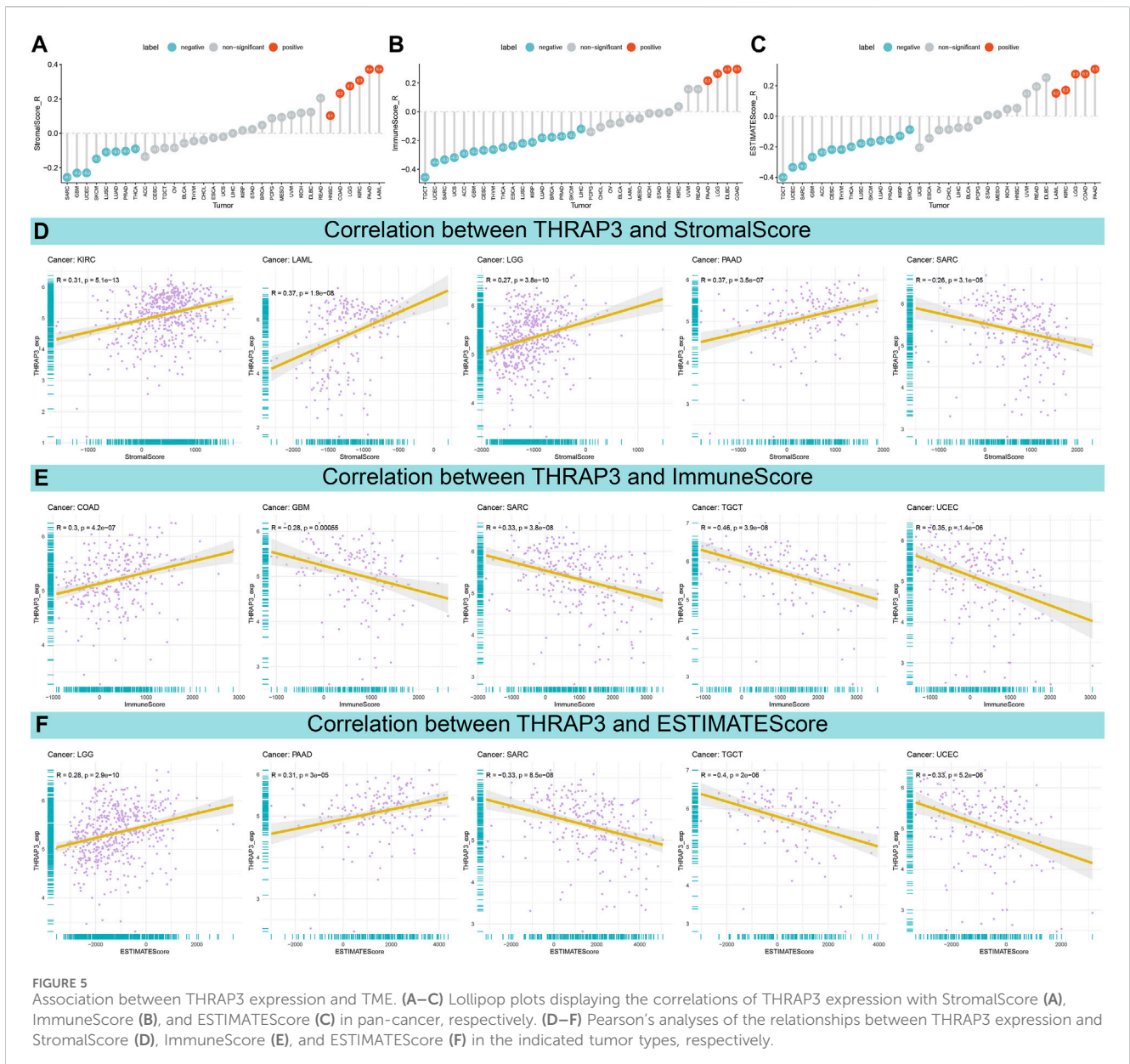
TME is a local homeostatic environment comprised of tumor cells, stromal cells, immune cells, extracellular matrix, and cytokines that develop alongside a tumor and provide the essential material

basis for tumor-related malignant phenotypes to develop (Pitt et al., 2016; Xiao and Yu, 2021; Hinshaw and Shevde, 2019).

StromalScore, ImmuneScore and ESTIMATEScore for each cancer were evaluated based on the R package “ESTIMATE (Yoshihara et al., 2013).” An analysis of the connection between THRAP3 and tumor immunity was conducted using the Pearson method. All results were depicted using the lollipop plot.

Enrichment analysis

Functional enrichment analysis was utilized to study the biological process of THRAP3 expression, and pathway enrichment analysis was used to explore cancer-related pathways of THRAP3 expression in various cancers. As a differential analysis at pathway levels, Gene Set Variation Analysis (GSVA) was used to investigate the difference in pathways between high- and low-THRAP3 subgroups (Hänzelmann et al., 2013). We carried out Gene Set Enrichment Analysis (GSEA) (Subramanian et al., 2005) and GSVA based on the R packages “ReactomePA,” “org.Hs.e.g.,db,” “clusterProfiler,” “enrichplot,” and “GSEABase.” The GSEA and GSVA gene sets were downloaded from the MSigDB official website (Castanza et al., 2023).



Genetic alteration analysis and drug sensitivity analysis

Analysis of the alteration frequency of THRAP3 in pan-cancer was performed based on the cBioPortal database (Cerami et al., 2012). Drug sensitivity analysis was conducted to explore the correlation between THRAP3 expression and drugs in the CellMiner database (Luna et al., 2021).

Statistical analysis

We performed differential analysis of THRAP3 expression using the Wilcoxon test. The correlation analysis was evaluated with Pearson’s or Spearman’s methods. The analyses were conducted

with R software (version 4.2.1), and a p -value < 0.05 was deemed statistically significant.

Results

Expression of THRAP3 in various cancers

THRAP3 expression levels in normal tissues are depicted in Figure 1A using the GTEx database. The highest levels of THRAP3 expression are found in bone marrow, while the lowest levels are found in pancreatic tissue. Based on the CCLE data, THRAP3 expression levels in distinct tumor cell lines were measured and ranked from high to low (Figure 1B). THRAP3 is highly expressed in 12 tumors and lowly expressed in

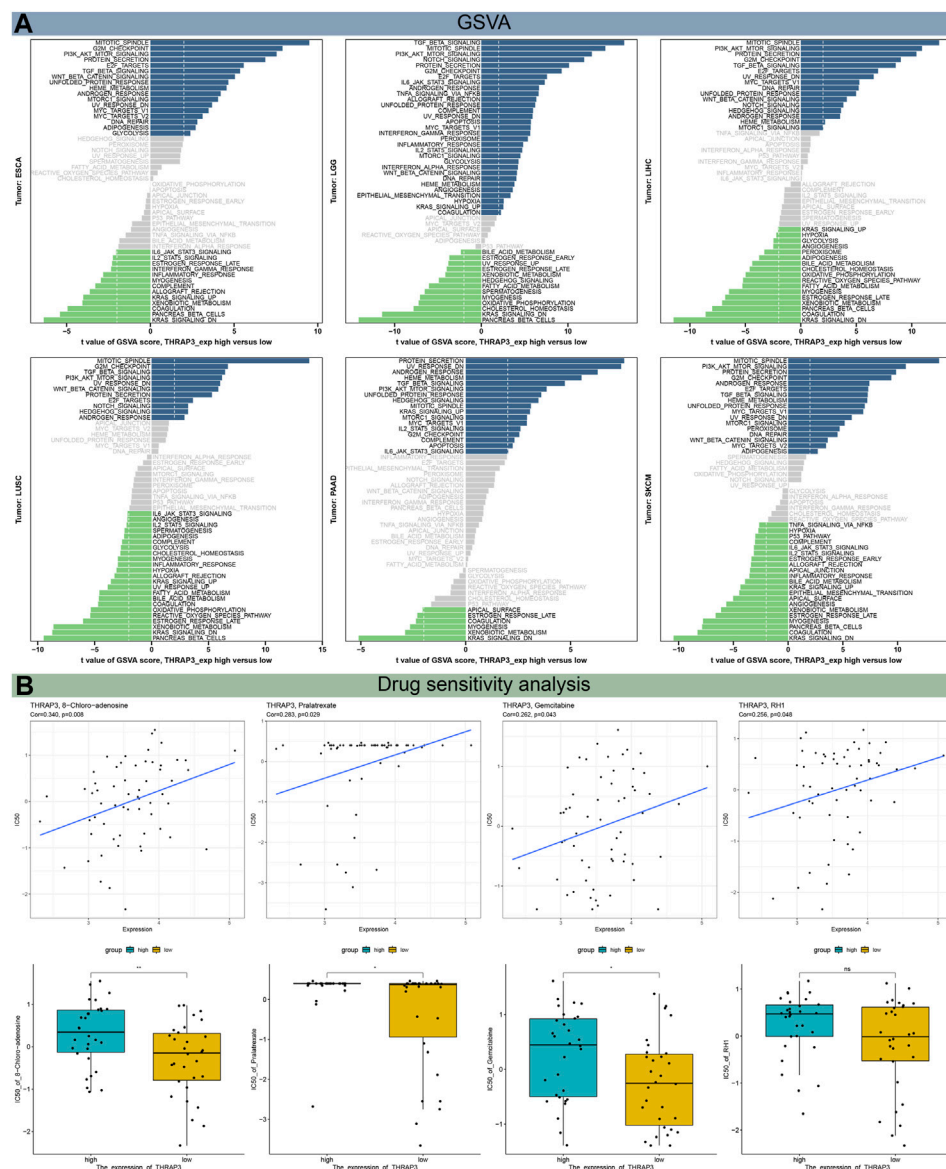


FIGURE 7 Results of GSEA (A) and drug sensitivity analysis (B).

Results of GSEA revealed that THRAP3 was predicted to be the activator of PI3K-Akt, TGF- β , Wnt- β pathways, G2M checkpoint, MYC targets V1, V2 (Figure 7A). Additionally, THRAP3 expression negatively correlates with myogenesis, xenobiotic metabolism, coagulation, pancreas- β cells in tumor patients with THRAP3 overexpression.

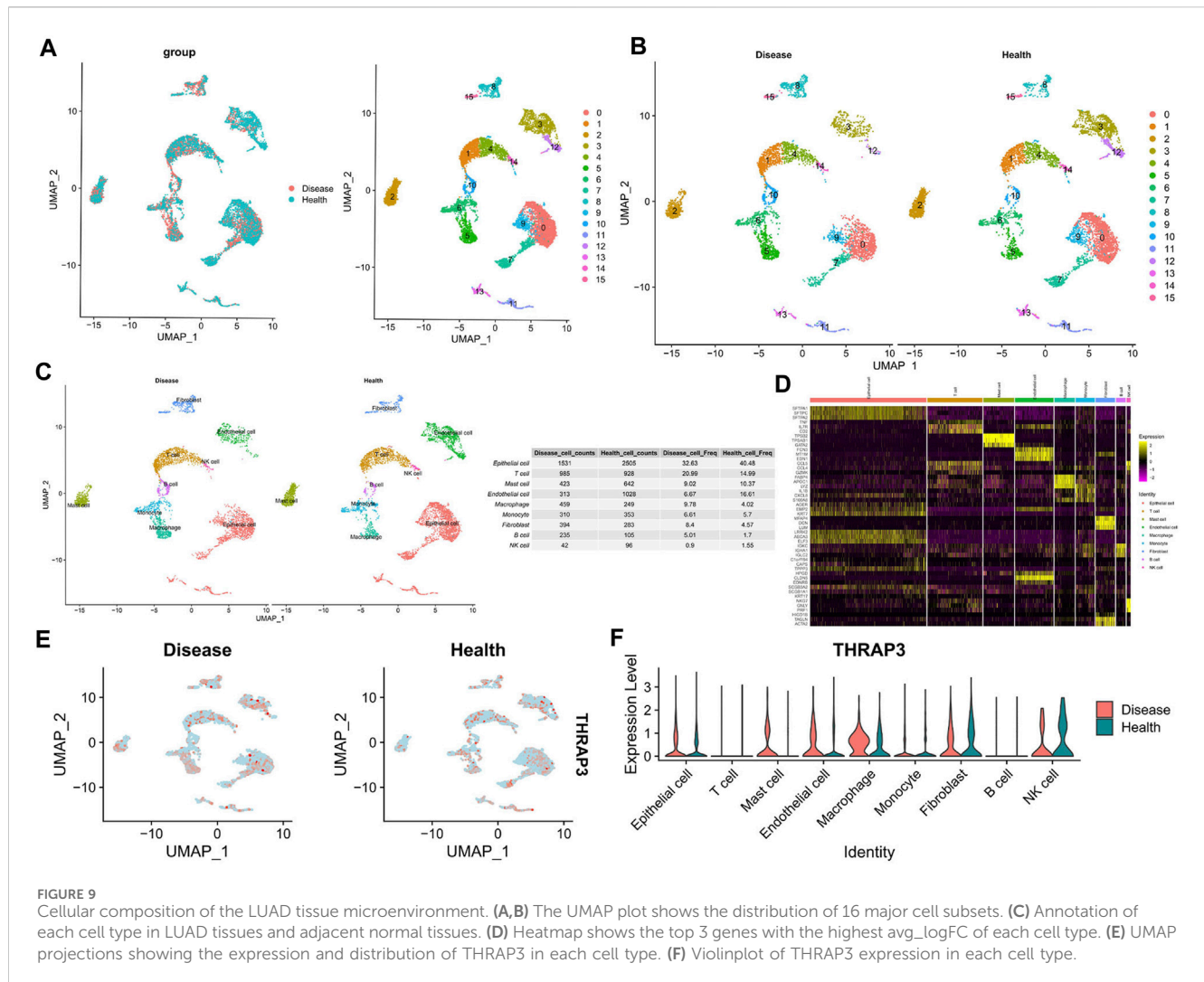
Genetic alteration analysis and drug sensitivity analysis

The mutation frequency of the THRAP3 gene in endometrial cancer, ovarian epithelial cancer, and melanoma exceeds 5%. Deep deletion is the only mutation type in miscellaneous neuroepithelial tumors (Figure 8A). Figure 8B illustrates that the mutation frequency of the THRAP3 gene was 2.7% in pan-cancer. Amplification and missense mutations are the most common mutation types.

Using the CellMiner data, we conducted a drug sensitivity analysis to determine the link between THRAP3 expression and the IC50 value of target medications (Figure 7B). The result showed that THRAP3 expression is positively connected with 8-Chloro-adenosine, Pralatrexate, Gemcitabine, RH1. Of note, patients with high THRAP3 expression have less sensitivity to 8-Chloro-adenosine, Pralatrexate, Gemcitabine.

scRNA profiling of LUAD

Following the pre-processing of the GSE149614 dataset, we combined LUAD with adjacent healthy tissues and then performed UMAP non-linear dimension reduction. Afterward, 16 cell subclusters were formed by segregating all cells (Figures 9A, B). The “FindAllMarkers” function was used to identify



early stage than at the late stage. Therefore, our data predict that ACC patients with high THRAP3 expression may have a poor prognosis. The forestplot data showed THRAP3 as a protective gene in KIRC, while in KICH, LGG, LUSC, KICH, BLCA, PAAD, ACC, and LIHC, THRAP3 is a high-risk gene. KM analysis further indicated that THRAP3 elevation had a longer survival time in KIRC. In comparison, upregulation of THRAP3 expression had a shorter survival in patients with KICH, LGG, SKCM, ACC, LGG. These results suggested that THRAP3 is a promising biomarker for tumors.

Next, we studied the relationship between THRAP3 expression and TME. The data showed that THRAP3 expression is negatively connected with StomalScore, ImmuneScore, ESTIMATEScore in most cancer types, including SARC, KIRC, LAML, LGG, PAAD, GBM, SARC, TGCT, UCEC, COAD. We hypothesize that THRAP3 plays an essential role in the formation of the TME.

Regarding the biological significance of THRAP3 expression in different cancers, THRAP3 was predicted to be a positive regulator of the lysosome, vacuole, centrosome, and cell growth, and to participate in regulating cancer-related pathways, including the PI3K-Akt, Hippo, MAPK, Rap1, calcium, hedgehog pathways. These results are worth further research.

Gene mutation analysis showed that THRAP3 gene mutations are prevalent in most cancer types. Three tumors with the highest alteration frequency of THRAP3 were endometrial cancer, ovarian epithelial cancer, and melanoma, respectively. Furthermore, tumor patients with THRAP3 overexpression have less sensitivity to 8-Chloro-adenosine, Pralatrexate, Gemcitabine based on the drug sensitivity data.

ScRNA-seq analysis revealed a significant increase in infiltration levels of T cells, macrophages, fibroblasts, and B cells in LUAD tissue compared to adjacent normal tissues, while THRAP3 was significantly upregulated in mast cells, endothelial cells, and macrophages. Our data suggests that the pathogenesis of LUAD involves alterations in both immune cell infiltration levels and THRAP3 expression.

Although we systematically analyzed the expression of THRAP3 in LUAD and evaluated the potential of THRAP3 to serve as a prognostic marker for LUAD, our study still has some limitations. Firstly, we did not thoroughly investigate the relationship between THRAP3 and immune cell infiltration. Secondly, the oncogenic role of THRAP3 in other tumors still requires further validation.

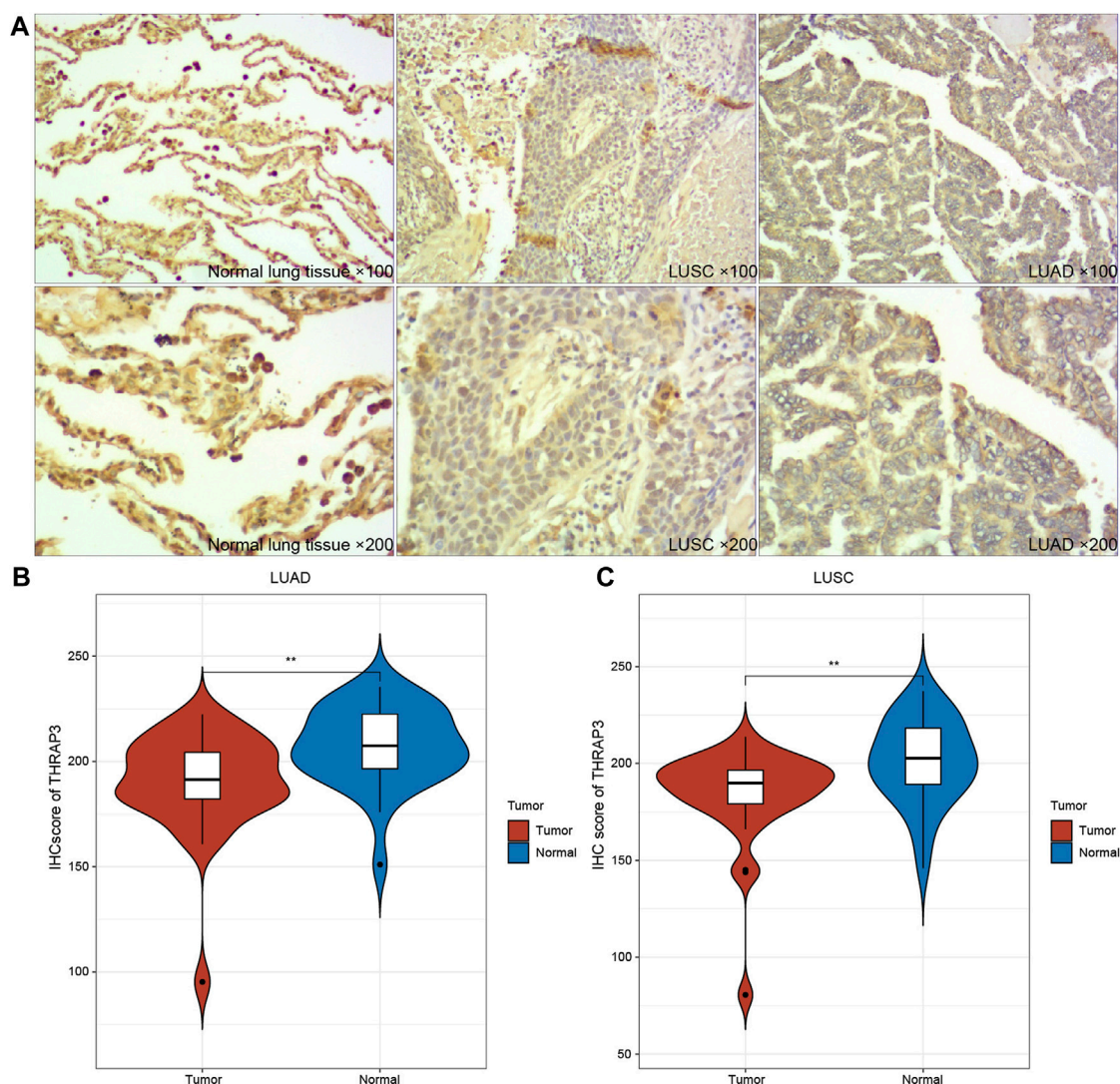


FIGURE 10 Immunohistochemical images of THRAP3 in LUSC, LUAD. **(A)** Low expression of THRAP3 in lung cancer tissues. **(B)** Differences in IHC scores between LUAD samples and normal samples. **(C)** Differences in IHC scores between LUSC samples and normal samples.

In conclusion

Our results reveal differential expression of THRAP3 in multiple cancers relative to matched-normal tissues, and THRAP3 could be a prognostic biomarker in specific cancer types. Based on the ScRNA-seq analysis, we speculate that mast cells, endothelial cells, and macrophages may affect the progression of LUAD by regulating THRAP3 expression.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding authors.

Author contributions

Y-PW: Writing–original draft. CM: Software, Writing–original draft, Writing–review and editing. X-KY: Writing–review and editing. NZ: Writing–review and editing. Z-GS: Writing–review and editing.

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The original data in our study were retrieved from the GEO database (<https://www.ncbi.nlm.nih.gov/geo>) and we gratefully acknowledge the contributions from public available databases.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgene.2024.1277541/full#supplementary-material>

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