Characteristics, clinical significance, and cancer immune interactions of lipid metabolism in prostate cancer

Zhipeng Xu[1]^, Xu Xu[1], Jianpeng Hu[1], Jian Tan[1], Yuanye Wan[1], Feilun Cui[2]

[1]Department of Urology, Affiliated People's Hospital of Jiangsu University, The First People's Hospital of Zhenjiang, Zhenjiang, China; [2]Department of Urology, Affiliated Taizhou Second People's Hospital of Yangzhou University, Taizhou, China

Contributions: (I) Conception and design: F Cui; (II) Administrative support: F Cui, J Hu; (III) Provision of study materials or patients: Z Xu, X Xu; (IV) Collection and assembly of data: Z Xu, X Xu, J Hu; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Feilun Cui, MD, PhD. Department of Urology, Affiliated Taizhou Second People's Hospital of Yangzhou University, 27 Jiankang Road, Taizhou 225300, China. Email: pdcuifeilun@163.com.

Background: The relationship between lipid metabolism, immune response, and immunotherapy in prostate cancer (PCa) is closely intertwined, and targeted intervention in lipid metabolism may facilitate the success of anticancer immunotherapy. This research attempted to explore effective immunotherapy for PCa.

Methods: We obtained RNA sequencing (RNA-seq) data for PCa patients from the UCSC Xena platform. Data analysis of differentially expressed genes (DEGs) was performed using package limma in R. Then, DEGs were subjected to enrichment analysis of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The Human Protein Atlas (HPA) database was conducted to validate the protein expression of the up-regulated lipid metabolism related genes (LMRGs) between PCa tissues and normal prostate tissues. And then we identified critical transcription factors (TFs), LMRGs and miRNA by constructing a regulatory network of TF-gene-miRNA. Furthermore, we determined the high and low groups based on the score of lipid metabolism enrichment. The hallmark gene sets were derived from gene expression profiles using the gene set variation analysis (GSVA) R package. Finally, we conducted immune infiltration analysis and drug sensitivity analysis.

Results: Immune response and lipid metabolism have undergone significant changes in PCa and paracancerous tissues compared to normal tissues. A total of 21 LMRGs were differentially up-regulated in PCa. The TF-gene-miRNA network showed that *PLA2G7*, *TWIST1*, and *TRIB3* may be the key genes that elevated lipid metabolism in PCa. The high group had more infiltration of B cell memory, macrophage M0, macrophage M1, and myeloid dendritic cell resting, and the low group had more infiltration of B cell plasma, monocyte, myeloid dendritic cell activated, and mast cell resting. The majority of checkpoint genes exhibited high expression levels in the low group. Lipid metabolism was remarkably correlated with drug sensitivity.

Conclusions: The analysis of lipid metabolism and related genes has revealed a complex regulatory mechanism that has a significant influence on immune response, immunotherapy, and medication guidance for patients with PCa.

Keywords: Prostate cancer (PCa); lipid metabolism; cancer immune; RNA sequencing (RNA-seq)

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^ ORCID: 0009-0009-5751-1112.

Introduction

Prostate cancer (PCa) is the most common cancer in terms of incidence and mortality among males in the urogenital system globally (1). For localized PCa, 10-year survival rate can be greater than 90% through radical prostatectomy or radiotherapy (2). Androgen deprivation therapy (ADT) is currently the primary approach for managing locally advanced and metastatic PCa (3,4). The majority of these patients will eventually progress to castration resistant PCa (CRPC) after undergoing ADT, and the combination of patient-specific immunotherapy and immune checkpoint inhibitors with conventional cytotoxic agents and therapies targeting the androgen receptor (AR) could be a viable option. Among them, the effectiveness of immunotherapy for CRPC has always been controversial in the past, however, as more mechanisms and targets are discovered, this approach has regained importance (5).

The exact causes of PCa remain unknown, but studies have suggested that individuals who are obese and on a high-fat diet have a higher risk (6). There was a positive correlation observed between the thickness of the prostate surrounding fat and the pathological staging and degree of invasion of PCa as revealed by prostate magnetic resonance imaging and transrectal prostate ultrasound examination (7). An elevated level of serum triglycerides was found to be linked with a higher likelihood of PCa recurrence (8). Studies have shown that PCa cells exhibit a higher rate of proliferation compared to normal cells, and have a greater demand for energy, with fat oxidation yielding significantly more adenosine triphosphate (ATP) than glucose (9,10). PCa cells have been found to rely more on fatty acid oxidation pathways for energy production, rather than glycolysis (11). *In vitro* study has demonstrated that upregulation of carnitine palmitoyltransferase 1A (CPT1A) in PCa cell lines LNCAP and C4-2 can enhance mitochondrial fatty acid oxidation and stimulate PCa cell growth (12). The transcriptomic and metabolomic data revealed a simultaneous increase in the expression of genes related to lipid metabolism and elevated levels of lipids in African-American PCa (13). These studies highlight the significance of lipid metabolism in the onset and progression of PCa.

Recent studies have found a close connection between lipid metabolism and the regulation of immune response (14-16). Additionally, lipid metabolism interventions have been discovered to hold promise as immunomodulatory agents and enhancers of anticancer immunotherapy (17). However, there has been no systematic study on the relationship between lipid metabolism, immune response, and immunotherapy in PCa. Here, we conducted a comprehensive analysis of the differences in lipid metabolism and associated genes between PCa tissues and normal tissues, as well as between PCa tissues and adjacent tissues. We analyzed the upstream transcription factors (TFs) and miRNAs that possibly target these associated genes, and then constructed the regulatory network of TF-gene-miRNA. Next, we assessed the correlations between these genes and immune cells, as well as immunotherapeutic effect. Furthermore, we obtained the score of lipid metabolism enrichment based on these genes, and analyzed the relationship with immune checkpoint, survival rate, recurrence rate, and drug sensitivity. This study is anticipated to make a valuable contribution towards the advancement of effective immunotherapies for PCa. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2140/rc).

Methods

Data acquisition

RNA sequencing (RNA-seq) data for PCa patients in The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression (GTEx) were obtained from the UCSC Xena platform (https://xenabrowser.net/datapages/), which contains 496 PCa tissues, 52 adjacent non-tumor tissues and 100 normal tissues. And miRNA-seq data were downloaded from the TCGA data portal (https://tcga-data.nci.nih.gov/

Highlight box

Key findings
- Lipid metabolism has a significant influence on immune response, immunotherapy, and medication guidance for patients with prostate cancer (PCa).

What is known and what is new?
- Lipid metabolism has a certain guiding significance for immunotherapy of PCa.
- This study collected the largest number of samples and groups, and comprehensively analyzed the impact of lipid metabolism on the immune response and immunotherapy of PCa.

What is the implication, and what should change now?
- A higher level of lipid metabolism may lead to reduced effectiveness of immunotherapy of PCa.

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tcga/), which contains 496 PCa tissues and 52 adjacent non-tumor tissues. The RNA-seq data used in this study were publicly available and obtained in accordance with TCGA guidelines, therefore no additional ethical approval was required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Differentially expressed genes (DEGs) and enrichment analysis

In order to identify the DEGs, R software (v4.2.1) was used to compare the expression profiles of PCa tissues with those of normal tissues, and also to compare the expression profiles of PCa tissues with those of paracancerous tissues. Data analysis of DEGs was performed using package limma (v3.52.3) in R (18), with thresholds of fold change (FC) ≥2 and adjusted P value <0.05 [$\log_2$ FC ≥1 and adjusted P value <0.05]. In order to further understand the biological function of DEGs, both the up-regulated and down-regulated DEGs were input into a database for annotation, visualization, and integrated discovery with clusterProfiler (v3.16.1) package in R [20] for Gene Ontology (GO) analysis, which includes the enrichment of biological processes (BP), cellular components (CC), and molecular functions (MF), as well as for Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis enrichment. The ggplot2 (v3.3.5) and simplifyEnrichment (v1.6.1) package in R were used to create the visual GO and KEGG enrichment maps generated by the annotation analysis.

Validation of protein expressions of the up-regulated DEGs involved in lipid metabolism

The Human Protein Atlas (HPA, https://www.proteinatlas.org/) database was conducted to validate the protein expression of the up-regulated lipid metabolism related genes (LMRGs) between PCa tissues and normal prostate tissues via using immunohistochemistry (IHC) (19).

Regulatory network of TF-gene-miRNA

In order to comprehensively and accurately explore the regulatory relationship between up-regulated LMRGs in PCa tissues and the upstream TFs and miRNAs that may target these genes, the potential miRNAs were predicted by miRTarBase, starBase2, miRWalk, and miRNANet. The upstream regulatory TFs enriched in DEGs were analyzed using package RcisTarget (v1.8.0) in R. Then, we analyzed

the Pearson's correlation coefficient (r) of TF-target genes and miRNAs-target genes, and filtered those with absolute r value >0.1 to construct regulatory network of TF-gene-miRNA.

Gene set variation analysis (GSVA)

GSVA is a nonparametric and unsupervised method for evaluating enrichment of transcriptome gene set. Using these up-regulated LMRGs as a set of hallmark genes for high expression of lipid metabolism in PCa. Calculating GSVA enrichment scores for gene sets representing lipid metabolism expression and dividing the scores into high and low groups based on the median value. The hallmark gene sets were derived from gene expression profiles using the GSVA R package (version 1.36.3), which utilized the cluster-averaged log-transformed expression matrix.

Immune infiltration analysis

To analyze the correlation between the high and low GSVA enrichment scores and immune cells infiltration. The immune cells infiltration of TCGA PCa samples were download from the Tumor Immune Estimation Resource 2.0 (TIMER2.0) (http://timer.cistrome.org/) which analyzed using CIBERSORT. The correlations between the two groups and immune cells infiltration were analyzed using Hmisc R package (version 4.7.1).

### Progression-free survival (PFS) and biochemical recurrence (BCR) analysis

To explore the correlation of the high and low GSVA enrichment scores and the survival and recurrence, we used survminer R package (v0.4.8) to perform PFS and BCR analysis.

Drug sensitivity analysis

To investigate the clinic performance of chemotherapy agents in patients, we computed the semi-inhibitory concentration (IC50) values of common drugs with package oncoPredict in R (20) based on Genomics of Drug Sensitivity in Cancer (GDSC, https://www.cancerrxgene.org/) database.

Statistical analysis

All statistical analyses were performed by R version 4.2.1
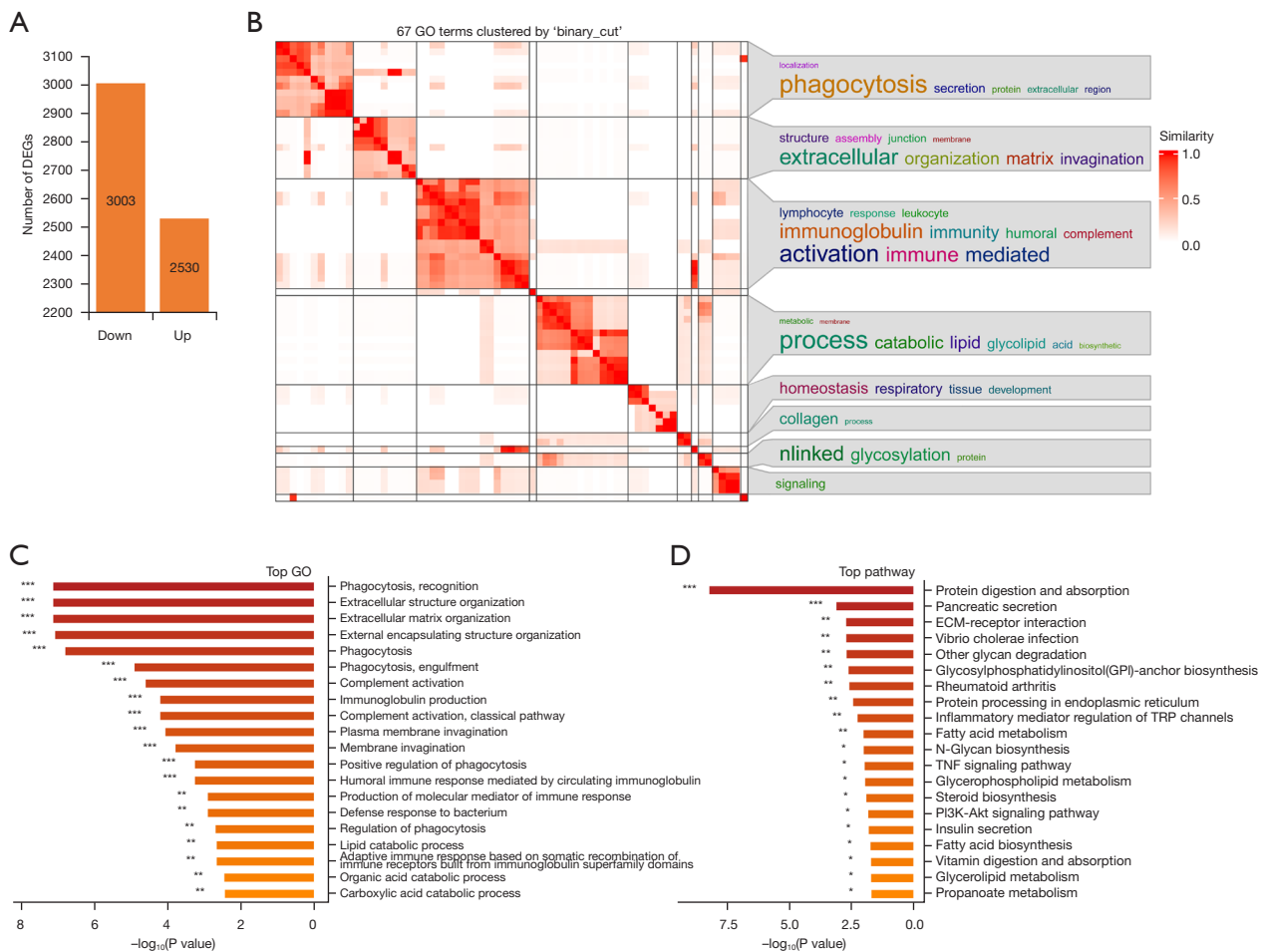
Figure 1 PCa and paracancerous tissues exhibit genetic and functional changes compared to normal tissues. (A) The number of down-regulated and up-regulated DEGs. (B) Clustering heatmap based on the GO enrichment results. (C) Top 20 biological process of GO terms of DEGs (***, P.adjust <0.001; **, P.adjust <0.01). (D) Top 20 KEGG pathways of DEGs (***, P<0.001; **, P<0.01; *, P<0.05). PCa, prostate cancer; DEG, differentially expressed genes; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; ECM, extracellular matrix; TRP, transient receptor potential; TNF, tumor necrosis factor.

(https://www.r-project.org/). Student's *t*-test and Wilcoxon rank-sum test were used in this study. Two-tailed P<0.05 was considered statistically significant. Data visualization was performed using the R package ggplot2 (v3.3.5). The heatmap was then plotted by the "pheatmap" package (v1.0.12) in R for visualization. Kaplan-Meier survival curves were created in each group, and log-rank tests were performed to compare the PFS and BCR between different groups. For correlation coefficients calculation, Pearson's correlation coefficient analyses were performed.

Results

PCa and paracancerous tissues exhibit genetic and functional changes compared to normal tissues

To uncover the characteristic changes of PCa and paracancerous tissues relative to normal prostate tissues, genes with significant differences between PCa and normal tissues but not significant differences between PCa and paratumor tissues were filtered from 496 PCa samples, 52 paracancerous tissues and 100 normal samples from the

UCSC Xena platform. A total of 5,533 DEGs (3,003 down-regulated, 2,530 up-regulated) were identified according to the fold change ≥2 and adjusted P value <0.05 cutoff criteria (*Figure 1A*). DEGs were then categorized to GO terms and KEGG pathways to discover biological functional changes in PCa and paracancerous tissues. The heatmap of GO enrichment results showed that phagocytosis, immunoglobulin, immunity, lipid, glycolipid, and homeostasis were highly enriched (*Figure 1B*). The top 20 most significant BP of GO terms showed that DEGs were enriched in phagocytosis, extracellular matrix organization, immune response, and lipid catabolic process (*Figure 1C*). The top 20 most significant KEGG pathways showed that protein digestion and absorption, inflammatory mediator regulation of TRP channels, and lipid metabolism related pathways (fatty acid metabolism, glycerophospholipid metabolism, steroid biosynthesis, fatty acid biosynthesis, glycerolipid metabolism) were highly enriched (*Figure 1D*). These results indicate that genes and biological functions, especially immune response and lipid metabolism have undergone significant changes in PCa and paracancerous tissues compared to normal tissues.

Lipid metabolism related biological functional and DEGs in PCa

Afterwards, we performed an DEGs analysis of PCa versus normal tissues and PCa versus paracancerous tissues, and obtained a total of 1,389 common DEGs (*Figure 2A*). GO enrichment analysis was performed according to the common DEGs. Up-regulated GO terms showed that lipid metabolism related BP (phospholipid catabolic, low-density lipoprotein particle remodeling, lipid catabolic process) were highly enriched (*Figure 2B*). Next, the up-regulated lipid metabolism related BP and genes were listed in detail (*Figure 2C,2D*). A total of 21 genes, including phospholipase A2 group IIA (*PLA2G2A*), phospholipase A1 member A (PLA1A), phospholipase A2 group VII (*PLA2G7*), arachidonate 15-lipoxygenase (*ALOX15*), twist family bHLH transcription factor 1 (*TWIST1*), angiopoietin like 3 (*ANGPTL3*), phospholipase A2 group IID (*PLA2G2D*), apolipoprotein C2 (*APOC2*), apolipoprotein C1 (*APOC1*), apolipoprotein E (*APOE*), glycerophosphodiester phosphodiesterase domain containing 1 (*GDPD1*), ELOVL fatty acid elongase 2 (*ELOVL2*), cytochrome P450 family 2 subfamily J member 2 (*CYP2J2*), nudix hydrolase 8 (NUDT8), TLC domain containing 1 (*TLCD1*), tribbles pseudokinase 3 (*TRIB3*), fatty acid synthase (*FASN*), acyl-CoA synthetase medium chain

family member 1 (*ACSM1*), solute carrier family 27 member 2 (*SLC27A2*), sphingomyelin phosphodiesterase acid like 3B (*SMPDL3B*), and alpha-methylacyl-CoA racemase (*AMACR*) were differentially up-regulated in PCa, indicating that these DEGs might be critical for elevated lipid metabolism in PCa. Then, the volcano plots were visualized to show the expression pattern of the up-regulated DEGs involved in lipid metabolism between PCa and normal tissues (*Figure 2E*), as well as PCa and paracancerous tissues (*Figure 2F*).

### *The protein expression levels of the up-regulated DEGs involved in lipid metabolism in PCa*

To determine the differentially protein expression of the up-regulated DEGs involved in lipid metabolism in PCa, representative images for IHC of the up-regulated LMRGs in PCa and normal prostate tissues were obtained from the HPA database. The results showed that the protein expression levels of NUDT8, FASN, ACSM1, and AMACR were higher in PCa tissues than that in normal prostate tissues (*Figure 3*). These outcomes were in consistent with the RNA-seq results.

### *Construction of TF-gene-miRNA regulatory network*

To explore the possible regulatory mechanism of these up-regulated LMRGs in PCa, we analyzed the upstream TFs and miRNAs that possibly target the DEGs, and then constructed the regulatory network of TF-gene-miRNA. The network showed that *PLA2G7*, *TWIST1*, and *TRIB3* may be the key genes that elevated lipid metabolism in PCa. And the up-regulated TFs, including NK2 homeobox 2 (*NKX2-2*), NFE2 like bZIP transcription factor 3 (*NFE2L3*), as well as the down-regulated TFs, including GATA binding protein 5 (*GATA5*), *MDS1* and EVI1 complex locus (*MECOM*), GATA binding protein 3 (*GATA3*), and retinoic acid receptor gamma (*RARG*) that regulated the three key genes, may play an important role in the regulation of lipid metabolism. Also, the predicted miRNAs (miR-205-5p, miR-1258, miR-204-5p) target *TRIB3* were down-regulated, indicating that these miRNAs might be critical for lipid metabolism in PCa (*Figure 4*).

Correlations between up-regulated LMRGs and immunity

Lipid metabolism is closely related to immune responses in PCa (21). In view of this, we analyzed the correlations between up-regulated LMRGs and immune cells. As
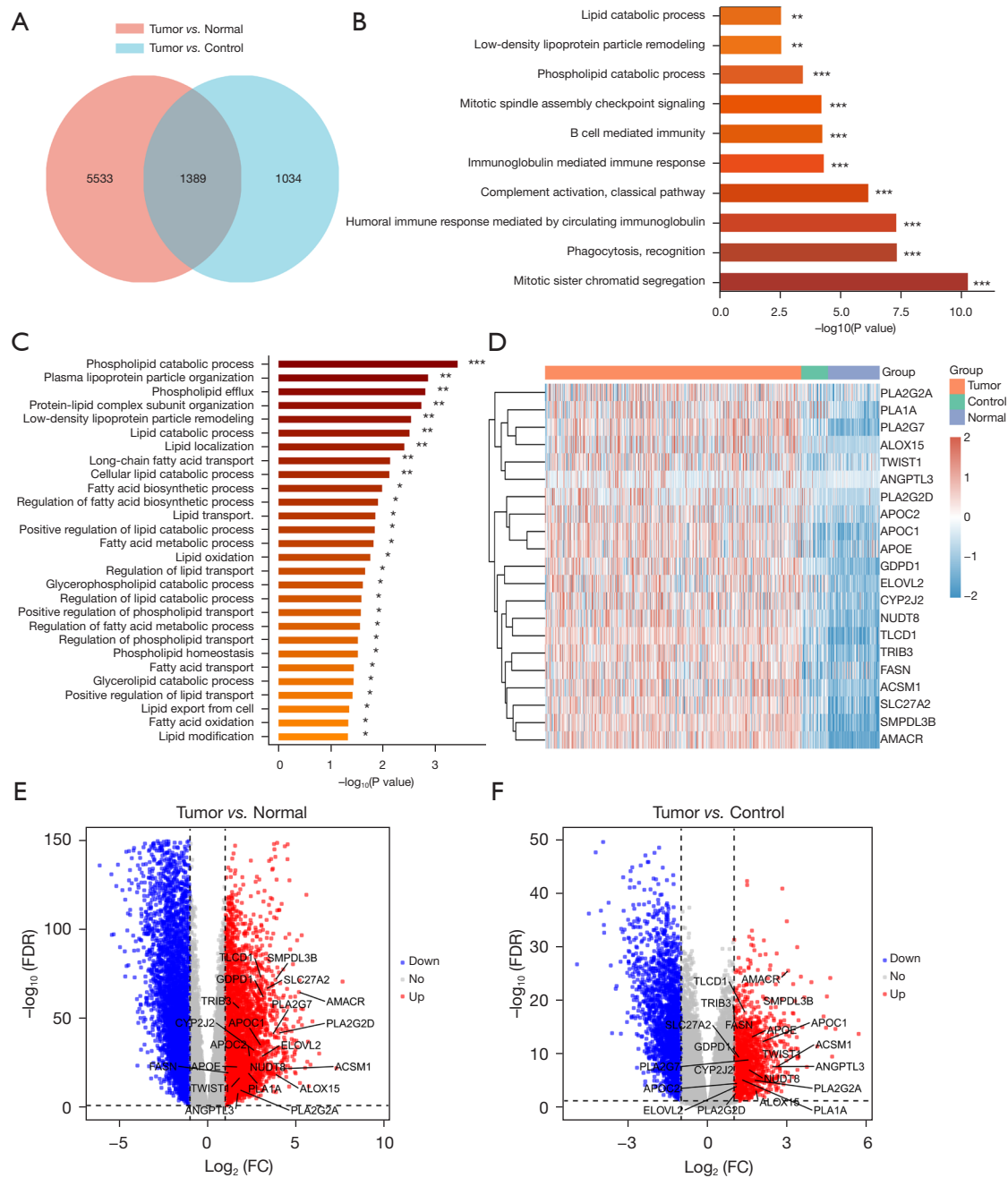
Figure 2 Lipid metabolism related biological functional and DEGs in PCa. (A) The Venn diagram of DEGs of PCa versus normal tissues and PCa versus paracancerous tissues. (B) Top biological process of GO terms of common DEGs (***, P<0.001; **, P<0.01). (C) List of main up-regulated lipid metabolism related biological processes. (D) The heatmap and hierarchical clustering of up-regulated lipid metabolism related genes. The expression levels of up-regulated lipid metabolism related genes were indicated by the color bar. Up-regulated genes were labeled in red color while down-regulated genes were labeled in blue color. (E) The volcano plots of DEGs between PCa and normal tissues, and marked the up-regulated lipid metabolism related genes. Red indicates high expression, and blue indicates low expression. Grey shows that those genes showed no difference between PCa and normal tissues. (F) The volcano plots of DEGs between PCa and paracancerous tissues, and marked the up-regulated lipid metabolism related genes. Red indicates high expression, and blue indicates low expression. Grey shows that those genes showed no difference between PCa and paracancerous tissues. DEGs, differentially expressed genes; PCa, prostate cancer; GO, Gene Ontology; FDR, false discovery rate.
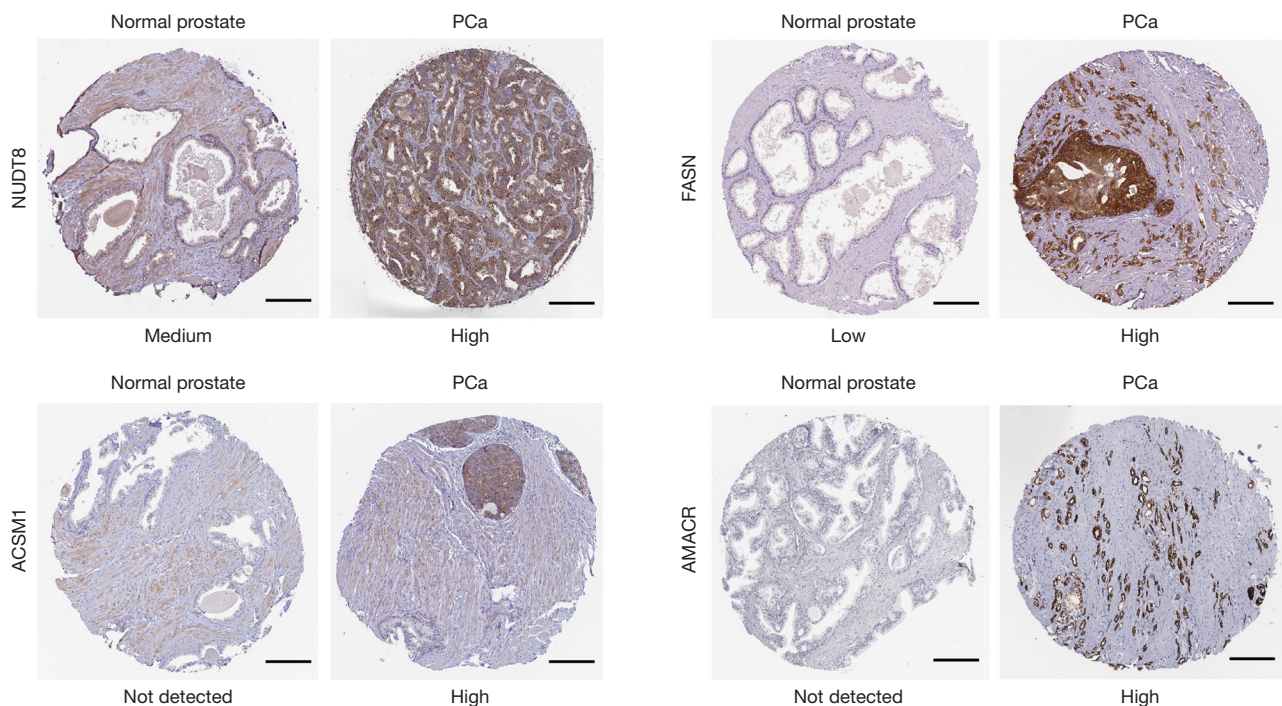
Figure 3 The protein expression levels of 4 up-regulated LMRGs by HPA database. Immunohistochemistry staining of NUDT8, FASN, ACSM1, and AMACR in normal prostate tissues and PCa tissues. High, medium, low and not detected represent the expression levels of proteins. Scale bar, 200 μm (Credit: Images from the HPA). Images available from v23.proteinatlas.org. The URLs for eight images are as follows: NUDT8 in normal prostate tissue, https://www.proteinatlas.org/ENSG00000167799-NUDT8/tissue/prostate#img; NUDT8 in PCa tissue, https://www.proteinatlas.org/ENSG00000167799-NUDT8/pathology/prostate+cancer#img; FASN in normal prostate tissue, https://www.proteinatlas.org/ENSG00000169710-FASN/tissue/prostate#img; FASN in PCa tissue, https://www.proteinatlas.org/ENSG00000169710-FASN/pathology/prostate+cancer#img; ACSM1 in normal prostate tissue, https://www.proteinatlas.org/ENSG00000166743-ACSM1/tissue/Prostate#img; ACSM1 in PCa tissue, https://www.proteinatlas.org/ENSG00000166743-ACSM1/pathology/prostate+cancer#img; AMACR in normal prostate tissue, https://www.proteinatlas.org/ENSG00000242110-AMACR/tissue/prostate#img; AMACR in PCa tissue, https://www.proteinatlas.org/ENSG00000242110-AMACR/pathology/prostate+cancer#img. LMRG, lipid metabolism related gene; HPA, Human Protein Atlas; PCa, prostate cancer.

depicted in *Figure 5A*, the up-regulated LMRGs were positively associated with the infiltration of macrophage M0, macrophage M1, myeloid dendritic cell resting, and T cell regulatory (Tregs), while the opposite performance was noted in relationship with the up-regulated LMRGs and B cell plasma, T cell CD8$^+$, and myeloid dendritic cell activated. We then divided the sample into high and low expression groups using the median of a single gene and analyzed the relationship between these two groups and immune cell. The results showed that the higher the expression of *PLA2G7*, *ALOX15*, *PLA2G2D*, and *APOC1*, the stronger the positive correlation with macrophage M1, myeloid dendritic cell resting, T cell regulatory (Tregs), and macrophage M2, respectively (*Figure 5B*). To explore

whether these LMRGs are related to immunotherapy, the correlations between these genes and the biomarkers for immunotherapy were displayed in *Figure 5C*. It was demonstrated that most genes were negatively correlated with the expression of immunotherapy biomarkers, except for *PLA2G2D*, *APOC1*, *APOC2*, and *APOE*.

Association of the enrichment of lipid metabolism with immune cells and immune checkpoints

Subsequently, LMRGs were used as a marker gene set for high expression of lipid metabolism in PCa. And we calculated the GSVA enrichment score, which represents the score of lipid metabolism enrichment. Then we divided
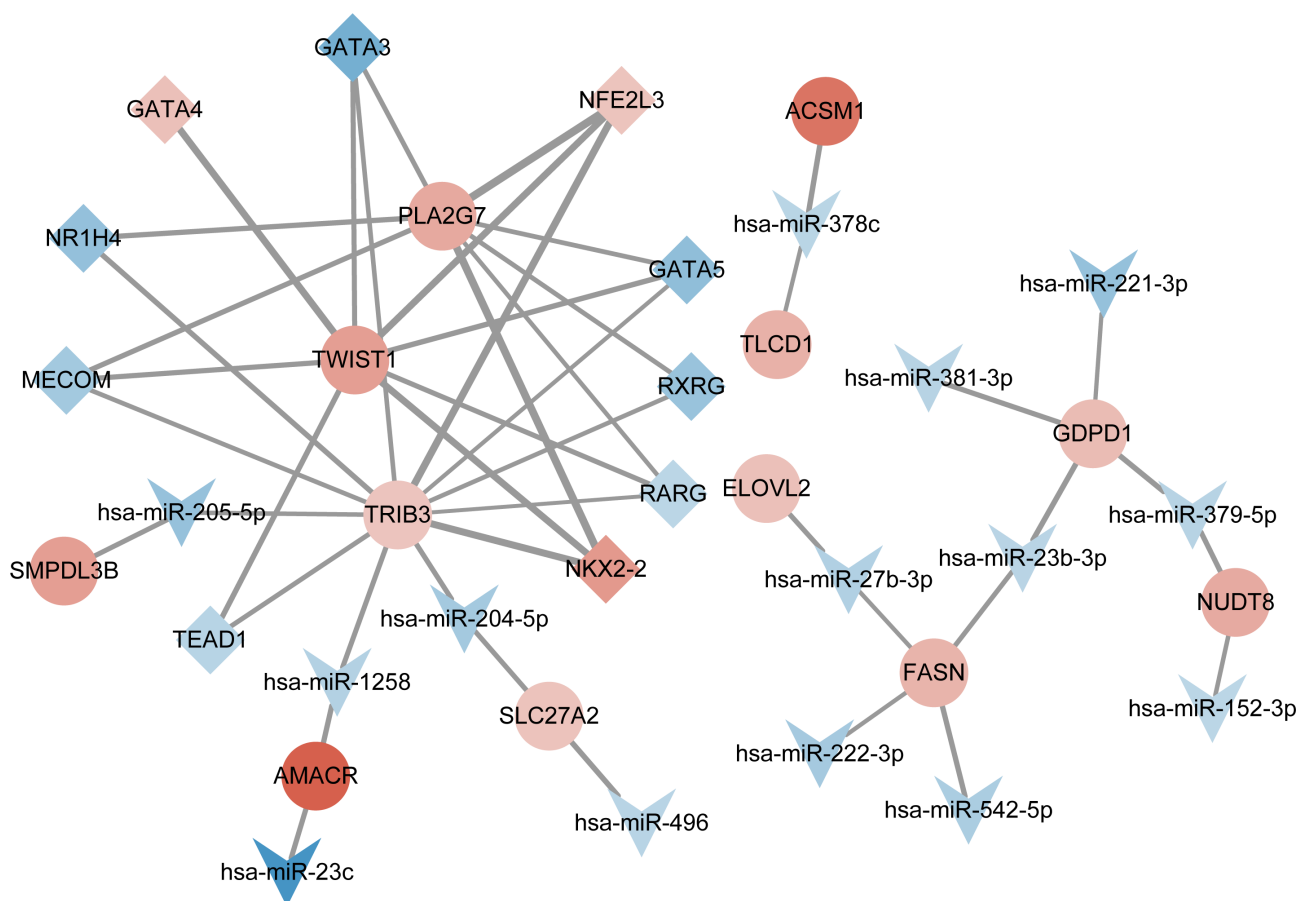
Figure 4 Construction of TF-gene-miRNA regulatory network. The network showing the connections and interactions among up-regulated LMRGs (circle), TFs (rhombus) and miRNAs (arrowhead). Red indicates high expression, and blue indicates low expression. The thicker the line, the stronger the correlation between the two, and vice versa. LMRG, lipid metabolism related gene.

the sample into high and low groups based on the median score. The correlations between the two groups and immune cells infiltration were analyzed using Hmisc R package. The results showed that the high group had more infiltration of B cell memory, macrophage M0, macrophage M1, and myeloid dendritic cell resting, and the low group had more infiltration of B cell plasma, monocyte, myeloid dendritic cell activated, and mast cell resting (*Figure 6A*). Additionally, we assessed the relationship between the two groups and immune checkpoints. *Figure 6B* demonstrates that most checkpoint genes are highly expressed in the low group, such as *CD274*, *ICOSLG*, *PDCD1LG2*, *TMIGD2*, *VTCN1*, *CD40*, *TNFRSF4*, *ENTPD1*, *LAG3*, *NT5E*. Then, the gene expression levels of these checkpoints in different groups were displayed in a heatmap (*Figure 6C*).

The impact of the enrichment of lipid metabolism on survival and recurrence

To explore the impact of the enrichment of lipid metabolism on survival and recurrence in PCa patients, we conducted PFS and BCR analysis across different groups. There was no significant difference in PFS and BCR between the high and low group (*Figure 7A*,*7B*).

Drug sensitivity analysis

Drug therapy, such as chemotherapy, targeted therapy, and immunotherapy may limit PCa progression and improve patients' prognoses (22). To identify the efficacy of the score of lipid metabolism enrichment as a biomarker to predict therapeutic response in PCa, we estimated
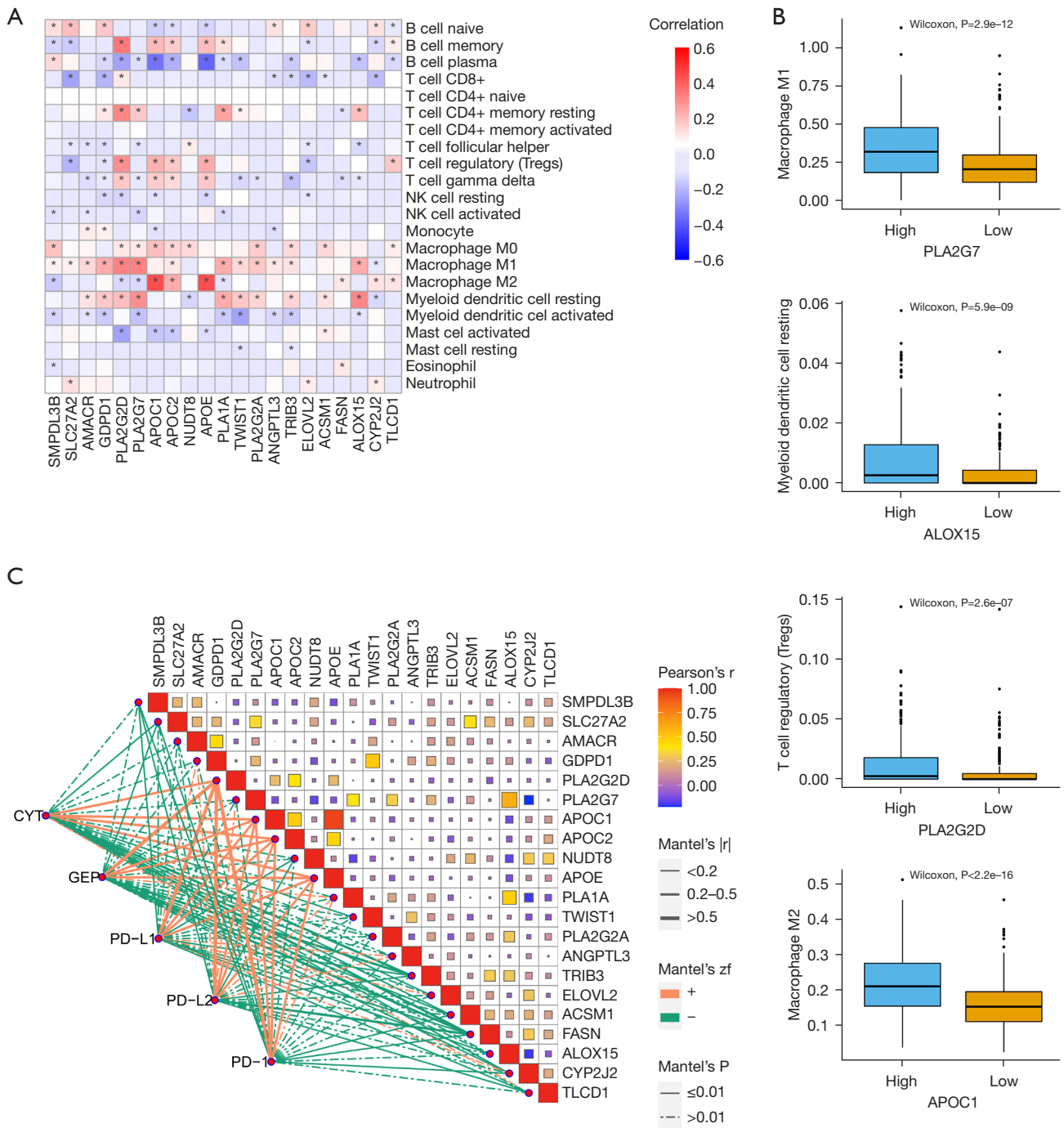
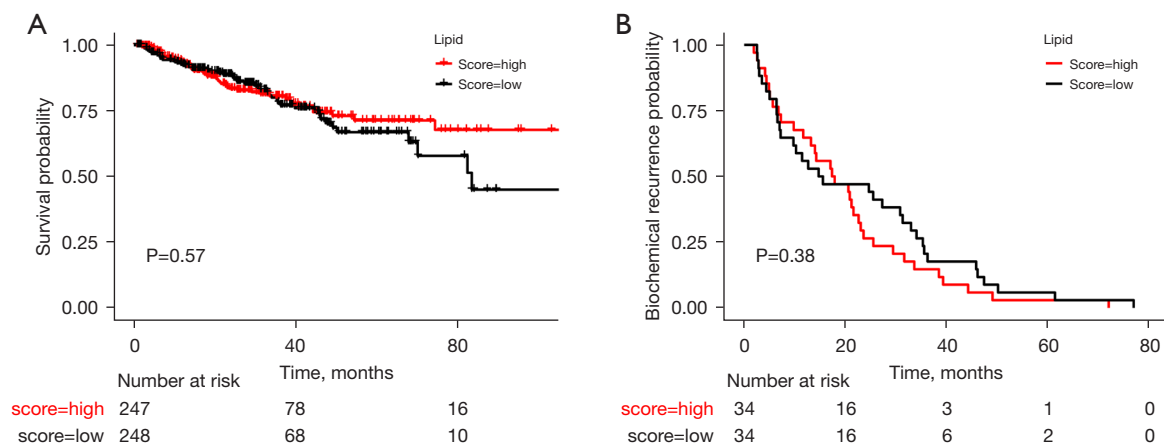**Figure 5** Correlations between up-regulated LMRGs and immunity. (A) The heatmap of correlations between up-regulated LMRGs and 22 types of immune cells. Positive correlation was labeled in red color while negative correlation was labeled in blue color (*, P<0.05). (B) Correlation between selected gene and immune cell. (C) Correlations between the up-regulated LMRGs and immunotherapy biomarker. The redder the color, the greater the Pearson's correlation coefficient, and the purpler the color, the smaller the Pearson's correlation coefficient. Positive correlation was labeled in orange color while negative correlation was labeled in green color. LMRG, lipid metabolism related gene.

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Figure 6 Association of the enrichment of lipid metabolism with immune cells and immune checkpoints. (A) The correlations between the two groups and immune cells infiltration. (B) The gene expression levels of immune checkpoints in the high and low groups. (C) The heatmap of immune checkpoints in different groups. The gene expression levels of immune checkpoints were indicated by the color bar. Red indicates high expression, and blue indicates low expression. ns stands for no significance, P>0.05; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.

the IC50 values of 160 drugs from GDSC dataset. We discovered that patients with high score of lipid metabolism enrichment may positively react to mitoxantrone, alisertib, topotecan, nelarabine, and foretinib, while patients with low score of lipid metabolism enrichment positively react to docetaxel, sorafenib, oxaliplatin, acetalax, and dabrafenib (*Figure 8A-8J*). These findings indicated that lipid metabolism was correlated with drug sensitivity.

Discussion

In this study, we analyzed the TCGA and GTEx cohorts

to determine the changes in transcription and expression of lipid metabolism and LMRGs, and further identified the relationship with immune infiltration, survival rate, recurrence rate and immunotherapy.

Emerging studies contributed to the discovery of lipid metabolism disorder in PCa. For instance, Li *et al.* collected PCa and adjacent nontumor (ANT) tissues and performed lipidomics and transcriptomics. They discovered significant disruptions in pathways related to the synthesis of lipids, the uptake of lipids, and the remodeling of phospholipids, which were associated with extensive lipid accumulation and alterations in lipid composition in PCa (23). The

Figure 7 The impact of the enrichment of lipid metabolism on survival and recurrence. (A) PFS analysis between the high and low group. (B) BCR analysis between the high and low group. PFS, progression-free survival; BCR, biochemical recurrence.

Figure 8 Drug sensitivity analysis. (A-J) Relationships between the score of lipid metabolism enrichment and drug sensitivity.

metabolism of cholesterol and lipids is significantly disrupted in PCa, with notable imbalances in the pathways responsible for fatty acid synthesis and oxidation (24). However, systematic analysis of PCa, adjacent and normal tissues remain largely undetermined, especially, the changes that occur in the adjacent tissues compared to normal tissues are not yet clearly explained.

Here, on the UCSC Xena platform, we identified 5,533 genes that exhibited significant differences between PCa and normal tissues, but not between PCa and paratumor tissues. These DEGs were found to be highly enriched in immune response and lipid metabolism, suggesting that

significant alterations have occurred in these pathways in paracancerous tissues. Keeping track of these DEGs or related metabolic indicators can be highly important in terms of preventing and detecting issues at an early stage. Further analysis showed that the expression level of LMRGs, including *PLA2G7*, *AMACR*, *TLCD1* and *SLC27A2*, gradually increased in normal, paracancerous, and PCa tissues. Consistently, a previous study has shown that *PLA2G7* is associated with aggressive PCa and promotes PCa cell migration and invasion (25). However, the mechanism by which *PLA2G7* regulates these phenotypes is still unclear. Our analysis revealed that

TFs *NKX2-2* and *NFE2L3* may regulate *PLA2G*7 in PCa. Unfortunately, there were no further experimental data to verify it. Similarly, the expression level of *AMACR* was coincident with previous research (26,27).

Cao *et al.* provided evidence of increased *FASN* expression in PCa tissues, which correlated with higher Gleason scores and clinical stages. Furthermore, *FASN* emerged as an independent prognostic biomarker for shorter BCR-free survival, as revealed by both univariate and multivariate analysis (P<0.05) (28). Additionally, it was demonstrated that the activity of *FASN* promotes cell motility driven by hepatocyte growth factor (*HGF*) in PCa, thereby enhancing the migration of cancer cells (29). In this study, *FASN* was also found to be upregulated differentially in PCa. These findings suggested that *FASN* may serve as a potential biomarker for predicting the prognosis of PCa.

It was worth noting that, NUDT8, a novel CoA-degrading enzyme that localizes to the mitochondria (30), was identified to be LMRG and significantly up-regulated in PCa in our study. CoA played a crucial role in various metabolic pathways such as the tricarboxylic acid cycle, fatty acid β-oxidation, lipogenesis, acetylcholine synthesis, and ketone synthesis and oxidation (31,32). NUDT8 was more likely to downregulate lipid metabolism based on these results. In actuality, it is the reverse. This could be attributed to the fact that NUDT8 participates in the lipid metabolism of PCa through various pathways.

Lipid metabolism plays an important role in controlling the immune system in the tumor microenvironment (33). The reprogramming of lipid metabolism can have a significant impact on the fate and function of immune cells. Altered lipid metabolism may have an impact on the immune function of natural killer T cells (NKT) that is both dependent and non-dependent on NKT cells (34). Specific lipid mediators play a critical role in determining the M1 and M2 phenotypes of macrophages (35). In Zhang's study, a six-gene signature related to lipid metabolism in PCa was developed to accurately predict prognosis and indicate the immune microenvironment status. They confirmed that patients in the high-risk subgroup had more infiltration of T cell CD4^{+} memory resting, Tregs, macrophage M0, and macrophage M1, while patients in the low-risk subgroup had more infiltration of monocyte and mast resting cell (36). Our finding was consistent with it. Additionally, we also demonstrated that the group with higher lipid metabolism showed a downtrend in the expression of immune checkpoint genes. This indicated that a higher level of lipid metabolism may lead to reduced effectiveness of immunotherapy. Finally, we also analyzed the correlation between lipid metabolism and drug sensitivity. Our data suggested that lipid metabolism can serve as a clinical guide for medication in PCa treatment, as patients with low lipid metabolism enrichment scores have shown a favorable response to docetaxel, which has traditionally been the primary chemotherapy drug used (37). These findings contribute to the identification of novel approaches for targeted therapy in PCa.

Lucarelli *et al.* reported novel genomic drivers of the lipid metabolism in PCa: PDHA1 and PDP1, which frequently exhibit amplification at both the gene and protein levels in primary PCa, particularly in high-grade tumors (38). Our analysis also revealed a significant upregulation of *PDP1* in PCa, while no significant difference was observed in *PDHA1* expression (the supplementary tables are available at https://cdn.amegroups.cn/static/public/tcr-23-2140-1.xlsx; https://cdn.amegroups.cn/static/public/tcr-23-2140-2.xlsx). This discrepancy may be attributed to the lack of tumor grading information for the PCa patients in our dataset, potentially introducing a statistical bias in gene expression levels.

There are several limitations to this study, including the retrospective nature of the data obtained from public databases, which may be subject to inherent selection bias. Additionally, the inclusion of additional clinical variables is necessary to fully explore the clinical significance of the lipid metabolism enrichment score. Furthermore, further prospective studies and *in vivo* and *in vitro* experimental studies are needed to validate our findings.

Conclusions

In conclusion, our thorough examination of lipid metabolism and associated genes reveals a comprehensive regulatory mechanism that has a significant impact on immune response, immunotherapy, and medication guidance for patients with PCa. This study highlights the crucial clinical relevance of lipid metabolism and provides a valuable foundation for future investigations into personalized therapy for PCa patients.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2140/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2140/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2140/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, in including ensuring that issues related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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