Identification of a Novel Lipid Metabolism-Related Gene Signature in Prognosis of Bladder Cancer

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Research

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Abstract

Background

Bladder cancer (BLCA) is a destructive cancer with unfavorable prognosis. Mounting studies have demonstrated that lipid metabolism affected the progression and treatment of tumor. Therefore, we aimed to explore the function and prognostic value of lipid metabolism-related genes in patients with bladder cancer.

Methods

Lipid metabolism-related genes (LRGs) were acquired from Molecular Signature Database (MSigDB). LRG mRNA expression and clinical data were obtained from the Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) dataset. Cox regression analysis and least absolute shrinkage and selection operator (LASSO) regression analysis were used to identify the prognostic gene for predicting overall survival in BLCA. The Kaplan-Meier analysis was performed to assess the prognosis. The function of LRGs was explored via enrichment analysis and single sample Gene Set Enrichment Analysis (ssGSEA). CMAP database was used to find the small molecule drugs for treatment.

Results

We successfully constructed and validated a 11-LRG risk model for predicting the prognosis of BLCA patients. Furthermore, we also found that the 11-gene signature was an independent hazardous factor. Functional analysis suggested that LRGs were closely related with the PPAR signaling pathway, fatty acid metabolism and AMPK signaling pathway. LRGs were also involved in immune cells infiltration. Five small molecule drugs could be the candidate treatment for BLCA patients based on CMAP dataset.

Conclusion

In conclusion, we identified a reliable prognostic biomarker based on 11-LRG signature and found five small molecule drugs for BLCA patient treatments.

Introduction

Bladder cancer (BLCA) is one of the most common malignancies of the genitourinary system, and is also the 12th most common cancer worldwide[1]. The incident risk of BLCA is closely correlated with smoking[2]. According to the muscular invasion, BLCA can be classified into two types: non-muscle-invasive BLCA and muscle-invasive BLCA. The former is generally treated by transurethral bladder tumor resection (TURBT) and intravesical instillation regularly. However, it remains easy to recur and progress. The latter usually requires radical cystectomy and urinary diversion, even chemotherapy, immunotherapy, and targeted therapies. Worse, patient prognosis may remain unfavorable. Therefore, it is essential to identify early diagnostic and prognostic biomarkers to improve the curative effects of BLCA.

Emerging evidence has confirmed that aberrant metabolic reprogramming, especially glycolysis[3, 4], mitochondrial oxidative phosphorylation[5, 6], cholesterol metabolic pathways[7], and fatty acid metabolism[8], contributed to the occurrence of many diseases, including cancers and inflammation[9]. Lipids are not only one of the three nutrients necessary for normal cell growth but also components of cell membranes, which determine the significant effect of lipids in cell growth and homeostasis. Recently, lipid metabolism disorder has been regarded as one of the most significant metabolic hallmarks of tumor cells[10, 11]. They not only provide nutrition for the malignant proliferation of tumor cells but also can be in favor of tumor cells to adapt to microenvironmental changes. Bladder carcinogenesis are associated with alterations in lipid metabolism[12–14]. Overexpression of fatty acid synthase (FASN) has been found to be negatively correlated with OS and recurrence[15]. Furthermore, silencing FASN significantly suppressed the proliferation and invasion of BLCA cells by AKT/mTOR signaling pathway[16]. FASN may contribute to chemotherapy resistance[17].

In the present study, we firstly obtained genes associated with lipid metabolism and systematically analyzed their potential mechanisms. Then, we identified small molecule compounds that target lipid metabolism related genes for BLCA treatment. Above all, we revealed the relationship between these genes and overall survival (OS) of BLCA. Finally, we constructed an 11 lipid metabolism-related genes prognostic model, which can accurately predicted BLCA patient prognosis. Our results indicated that lipid metabolism may be a promising treatment direction for BLCA.

Materials And Methods

TCGA-BLCA Cohort and GEO Cohort

we downloaded the level-three transcriptome RNA sequencing data and corresponding clinicopathological characteristics of bladder cancer patients from the Cancer Genome Atlas (TCGA) data portal (<https://gdc-portal.nci.nih.gov/>). Meanwhile, GSE13507 was used as validation sets, which obtained Illumina Human-6 v2.0 Expression BeadChip platform in Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>).

Lipid metabolism gene set

Four lipid metabolism data sets (Reactome metabolism of lipids, Reactome phospholipid metabolism, Hallmark fatty acid metabolism, and Kyoto Encyclopedia of Genes and Genomes (KEGG) glycerophospholipid metabolism) were acquired from the Molecular Signature Database v7.1 (MSigDB; <https://www.gsea-msigdb.org/gsea/msigdb>).

Identification of differentially expressed lipid metabolism-related genes

Limma package of R (version R 3.6.1, <https://bioconductor.org/packages/release/bioc/>) was used to screen the differentially expressed lipid metabolism-related genes (DELRGs) between BLCA and normal samples. False discovery rate (FDR) < 0.05 and |log2 fold change (FC)| > 1 were set as the cut-off criteria.

Enrichment Analysis of DELRGs

To further investigate the potential molecular mechanisms involved by DELRGs, Gene ontology (GO) and pathway enrichment analysis of DELRGs were performed by the clusterProfiler R package. P and FDR values < 0.05 were considered statistically significant.

Identification of potential small molecule drugs

The connectivity Map (CMAP) database (<http://www.broadinstitute.org>) was used to forecast a potential drug that may reverse or induce the biological states of BLCA based on DELRGs. We submitted the DELRGs to the CMAP database and searched for small molecular drugs for BLCA treatment. The enrichment scores ranged from -1 to 1. A negative score suggested that the drug could be beneficial for BLCA treatment.

Construction and validation of LRGs Prognostic Signature

Univariate Cox regression was used to identify the prognostic value of LRGs in BLCA. Then, we used Lasso regression to select potential risk genes and eliminate genes that would overfit the model. Finally, we performed multivariate Cox regression analysis and established an optimized risk score model. Kaplan-Meier curve was plotted to evaluate the significant difference in survival outcomes between high risk and low risk groups. The survival ROC package was used to conduct the receiver operating characteristic curve (ROC). The prognostic model was externally validated using the GEO dataset to test its stability.

Validating the performance of the prognostic model

We conducted univariate and multivariate Cox regression to determine if the prediction of LRGs prognostic signature was independent of clinical variables. A nomogram survival model was established using the R package rms based on the independent prognosis-associated LRGs to predict the survival rate of BLCA patients at 3 and 5 years. The nomogram and calibration curve were plotted by performing the "rms" R package. We estimated the accuracy of the nomogram by calculating the consistency index between the actual observation frequency and the predicted probability. The calibration curve was utilized to visualize the performance of the nomogram.

The prognostic model and immune infiltration

We further assessed the cell fractions of 16 immune cells and immune-related pathways via performing the single-sample gene set enrichment analysis (ssGSEA) achieved through the "gsva" package. The immune-related gene sets utilized are provided in table.

Result

Identification of DELRGs in BLCA

The RNA-seq levels of 857 LRGs in BLCA (n = 414) and normal bladder tissues (n = 19) in TCGA were acquired. We identified 113 DELRGs with $FDR < 0.05$ and $|\log_2 FC| > 1$ as the screening criteria, including 49 downregulated and 64 upregulated genes (Figures 1A and B).

Functional enrichment analysis of DELRGs

Functional enrichment analysis was performed with the 113 DELRGs. In the biological processes (Figure 2A), the DELRGs were mainly enriched in steroid metabolic process, fatty acid metabolic process, lipid catabolic process, steroid biosynthetic process, and fatty acid derivative metabolic process. In the cellular components (Figure 2A), the DELRGs were mainly enriched in lipid droplet, peroxisomal matrix, myelin sheath, microbody lumen, peroxisome, and microbody. In the molecular functions (Figure 2A), the DELRGs were mainly enriched in cofactor binding, monooxygenase activity, iron ion binding, phospholipase A2 activity, and NADP binding. In the KEGG pathways, the results showed that the DELRGs were mainly enriched in glycerophospholipid metabolism, PPAR signaling pathway, fatty acid metabolism, and AMPK signaling pathway (Figure 2B).

Analysis of small molecular drugs

To identify candidate small molecular drugs for treating BLCA, all DELRGs were divided into up-regulated and down-regulated groups, which were uploaded to the CMAP database. We identified five small molecular drugs with anti-cancer functions in the BLCA progression (enrichment score < 0) with $p < 0.01$ and $n > 2$ as the screening criteria. Table 1 shows the 5 small molecule drugs.

Construction of LRGs signature for predicting OS

29 DELRGs were associated with the prognosis of BLCA patients through univariate Cox regression analysis (Figure 1C). To ensure the stability and feasibility of clinical prognosis based on 29 genes, we obtained 19 DELRGs associated with the prognosis of BLCA patients by lasso survival analysis (Figure 3A and B). After multivariate Cox

regression analysis, 11 genes were identified and used to construct a prognostic signature for OS (Figure 4E). 11 genes, including FASN, MBOAT7, SERPINA6, PPARGC1B, FADS1, CPT1B, HSD17B1, OSBPL10, AKR1B1, CCDC58, and PLA2G2F, were selected to construct LRGs signature for predicting OS. We developed a 11 genes signature-based risk score based on their COX coefficient as follows:

$$\text{Risk score} = (0.2728 \times \text{FASN expression}) + (-0.2101 \times \text{MBOAT7 expression}) + (0.8956 \times \text{SERPINA6 expression}) + (-0.3559 \times \text{PPARGC1B expression}) + (0.1154 \times \text{FADS1 expression}) + (-0.2844 \times \text{CPT1B expression}) + (0.1872 \times \text{HSD17B1 expression}) + (0.193 \times \text{OSBPL10 expression}) + (0.1156 \times \text{AKR1B1 expression}) + (-0.2434 \times \text{CCDC58 expression}) + (0.064 \times \text{PLA2G2F expression})$$

Patients were then divided into high- and low-risk groups on the basis of the median value. Patients in the high-risk group showed poorer prognosis than those in the low-risk group ($p < 0.05$) (Figure 3C, E and G).

Time-dependent ROC analysis indicated that the prognostic accuracy of the 11 LRGs signatures in the discovery set was 0.716 at 5- year (Figure 3I).

Validation of the LRGs signature in GEO dataset

To ensure the prediction value of the LRGs signature, we used GSE13507 as validation sets to validate our results. According to the LRGs-based classifier identified above, BLCA patients in the validation sets were divided into a high- and a low-risk group by the median risk score. In accord with the results from above, significantly higher survival rates were observed in low-risk groups compared with the high-risk ones in the validation set (Figure 3D, F and H). Time-dependent ROC analysis indicated that the prognostic accuracy of the LRGs signatures was 0.721 at 5-year (Figure 3J).

Independent Prognostic Role of LRGs Signature

To explore the independence of the LRGs signature, we compared the clinical features including gender, age, grade, stage, T, N, and LRGs signature risk score by performing univariate and multivariate Cox regression analysis. Age (HR = 1.037, 95% CI = 1.020–1.055; $p < 0.001$), stage (HR = 1.783, 95% CI = 1.44–2.207, $p < 0.001$), T (HR = 1.569, 95% CI = 1.233–1.819, $p < 0.001$), N (HR = 1.548, 95% CI = 1.317–1.819, $p < 0.001$), and risk score (HR = 1.615, 95% CI = 1.424–1.832, $p < 0.001$) were significantly associated with OS in the univariate analysis (Figure 4A). Multivariate analysis suggested that age (HR = 1.032, 95% CI = 1.014–1.05, $p < 0.001$) and risk score (HR = 1.479, 95% CI = 1.298–1.685, $p < 0.001$) were also significantly associated with OS (Figure 4B). Therefore, this indicated that the risk score was an independent prognostic predictor. To better forecast the prognosis of BLCA patients, we constructed a nomogram from the variables associated with OS (Figure 4C). The calibration curve suggested that the nomogram showed good performance in consistent with between the nomogram's 3- or 5-year OS estimates and the Kaplan–Meier estimates (Figure 4D and E).

Analysis of immune infiltration

In order to define the relationships between the risk scores and immune infiltration, we investigated the enrichment scores of 16 immune cells and their participated pathways by using ssGSEA R package. The results revealed that immune cells (such as DCs, aDCs, pDCs, mast cells, B cells, CD8+ T cells, macrophages, Th2 cells, Th1 and Tfh cells, TIL cell, Neutrophils, Treg cells, T helper cells,) were remarkably elevated in the high-risk groups compared with low-risk group (Figure 5A). In addition, the scores of the immune-related pathways (such as the type I IFN response, parainflammation, type II IFN response, MHC class I, CCR, T cell co-inhibition, cytolytic activity, APC inhibition, inflammation-promoting and check-point) were also generally higher in high-risk group, indicating that their immunological functions related with lipid metabolism were more active in the high-risk group (Figure 5B).

Discussion

Significant advances in BLCA diagnosis and treatment have been achieved over the past two decades. However, the morbidity and mortality of BLCA remains unchanged owing to the aging of population and absence of specific therapy. Consequently, novel prognostic biomarkers and treatments for BLCA need to be identified to improve patient prognosis. Mounting studies have suggested that lipid metabolism dysregulation was involved in development and progression of various cancers, including lung cancer[18], prostate tumor[19], gastric carcinoma[20], BLCA[13], and so on. Despite lipid metabolism's crucial role in BLCA, studies about lipid metabolism with BLCA prognosis are few.

In the present study, we comprehensively investigated the potential mechanism and prognostic value of LRGs in BLCA through bioinformatic analyses. We initially acquired 113 DELRGs by analyzing the expression of LRGs in BLCA tissues compared with normal bladder tissues in TCGA dataset. Finally, we utilized the TCGA cohort to establish a BLCA prognostic risk signature by performing lasso regression analysis and univariate and multivariate Cox regression analysis. Meanwhile, GEO cohort was used to prove the specificity and sensitivity of this signature. We detected that a LRGs signature comprising of 11 LRGs (FASN, MBOAT7, SERPINA6, PPARGC1B, FADS1, CPT1B, HSD17B1, OSBPL10, AKR1B1, CCDC58, and PLA2G2F) could forecast the survival rate of BLCA patients.

Fatty acid desaturase 1 (FADS1) located in chromosome 11q12-11q13.1, was a member of the fatty acid desaturase gene family. Studies about FADS1 primarily focused on its polymorphisms and regard FADS1 as a rate limiting enzyme in the biosynthesis of long-chain polyunsaturated fatty acids precursors of eicosanoids[21]. FADS1 has been reported to play a crucial role in many diseases, including type-1 diabetes and cancer[22, 23]. FADS1 can promote the progression of laryngeal squamous cell carcinoma by activating the AKT/mTOR signaling pathway[24]. Reduced FADS1 expression has been related to poor prognosis in NSCLC patients[25]. Jiao reported that FADS1 overexpression was positively correlated with tumor grade in BLCA[26]. Further study has indicated that FADS1 knockdown inhibited BLCA cell proliferation by arresting cell cycle. Membrane bound O-acyltransferase domain containing 7 (MBOAT7) has been reported to play an important role in inflammation[27]. Heinrichs found that MBOAT7 might contribute to GC susceptibility through inflammation[28]. MBOAT7 was overexpressed in renal cancer cell and high MBOAT7 expression was associated with poor prognosis in ccRCC[29].CCDC58 may play a tumor-promoting role in endometrial cancer. Aldo-keto reductase 1 member B1 (AKR1B1) could be involved in various signaling pathways, such as epithelial to mesenchymal transition (EMT)[30], inflammatory responses[31], and mTOR pathway[32]. Growing study suggested that AKR1B was involved in cancer progression[33]. Carnitine palmitoyltransferase 1B (CPT1B) has been reported to be related with tumor proliferation and metastasis through regulating EMT in BLCA[34]. Overexpression of CPT1B was correlated with worse OS in prostate cancer[35]. Further study has revealed that AR-mediated CPT1B promoted castration-sensitive and castration-resistant prostate cancer (CRPC) progression by upregulating AKT expression and phosphorylation. Peroxisome proliferator-activated receptor gamma coactivator 1 beta (PPARGC1B) could increase its transcriptional activity by selectively interacting with ER α , which played a vital role in the ER signaling pathway[36]. PPARGC1B could inhibit miR-21 mediated fatty acid metabolism[37]. SERPINA6 was related to chemotherapy resistance in breast cancer[38].

Furthermore, we also found five potential small molecule drugs highly related to LRGs by using CMAP dataset for the treatment of BLCA patients. Flurbiprofen, a non-selective cyclooxygenase suppressor, was commonly used in anti-inflammation and pain control during surgery. Recently, flurbiprofen has been reported to exert anti-cancer effects through suppressing proliferation and inducing apoptosis in several tumors[39, 40]. Meclizine could inhibit breast cancer cells clonogenesis in vitro[41]. Alfuzosin, an alpha1-adrenergic receptor antagonist, which generally used for the treatment of hypertension and benign prostatic hyperplasia, reduced the growth of prostate tumor cells PC3[42]. Fenoprofen, a nonsteroidal anti-inflammatory drug, has been reported to relate to the incidence and metastases of prostate cancer[43]. Further research has shown that fenoprofen decreased the survival of prostate cancer cells by upregulating the expression of p75NTR (a neurotrophin receptor).

Conclusions

In conclusion, we identified a novel prognostic signature comprising of 11 genes involved in lipid metabolism in BLCA. In both training and validation sets, this signature could predict the overall survival of BLCA patients. Further research is essential in the future.

Abbreviations

BLCA
Bladder Cancer
LRGs
Lipid metabolism-related genes;
MSigDB
Molecular Signature Database
DELRGs
Differentially expressed lipid metabolism-related genes
TCGA
The Cancer Genome Atlas
GEO
Gene Expression Omnibus
KEGG
Kyoto Encyclopedia of Genes and Genomes
FDR
False discovery rate
FC
Fold change
GO
Gene ontology

Declarations

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Not applicable.

Authors' contributions

KZ, LX and WD designed the research study. LX and WD took responsibility for statistical analyses. KZ wrote the manuscript. WG and BF evaluated and revised the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

Competing interests

No competing interests.

Availability of supporting data

The data used to support the findings of this study are included in the manuscript.

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Tables

Table 1
the 5 small molecule drugs of CMP dataset analyses results

names of drugs	enrichment	<i>p</i> value	n	percent non-null
flurbiprofen	-0.947	0.00026	3	100%
meclozine	-0.911	0.00124	3	100%
alfuzosin	-0.894	0.00226	3	100%
ethotoin	-0.893	0.00234	3	100%
fenoprofen	-0.848	0.00699	3	100%

Figures

Figure 1

Differentially expressed LRGs in TCGA-BLCA set. (A) Heatmap showed differentially expressed LRGs; (B) Volcano presented of differentially expressed LRGs; (C) Univariate Cox regression analysis of differentially expressed LRGs.

Figure 2

Enrichment analysis of differentially expressed LRGs (A) GO analysis including biological process, cellular component and molecular function; (B) KEGG analysis.

Figure 3

The correlation between 11 LRGs risk signature and outcome of BLCA patients. (A) Lasso coefficient spectrum of the differentially expressed LRGs selected by the univariate Cox regression; (B) Seeking the best parameters for BLCA in the LASSO model (λ); (C-D) Kaplan-Meier survival analysis of BLCA patients between high-risk groups and low-risk groups in TCGA set (C) and GSE13507 set (D); (E-F) Time-independent receiver operating characteristic (ROC) analysis of risk scores predicting the overall survival

in TCGA set (E) and GSE13507 set (F);(G-H) Distribution of BLCA patients along with the arising of risk score in TCGA set (G) and GSE13507 set (H);(I-J) Distribution of survival status based on the median risk score in TCGA set (I) and GSE13507 set (J).

Figure 4

The risk signature was an independent prognostic factor for BLCA in TCGA set. (A) The correlations between the risk score for OS and clinicopathological factors by univariate Cox regression analysis; (B)

The correlations between the risk score for OS and clinicopathological factors by multivariate Cox regression analysis; (C) nomogram for predicting 3- or 5-year OS;(D) The calibration plots for predicting 3-year OS;(E) The calibration plots for predicting 5-year OS.

Figure 5

immune cells infiltration and correlated pathways between high-risk groups and low-risk groups. (A) immune cells infiltration between risk groups;(B) immune-related pathways between risk groups