Identification and validation of HSD11B2 as a biomarker for metastasis and prognosis of clear cell renal cell carcinoma

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Abstract

Background : Metastasis of clear cell renal cell carcinoma (ccRCC) is an important cause of death. The purpose of this study was to study the key gene in the process of tumor metastasis of ccRCC. **Methods :** Expression profiles of metastatic ccRCC and primary ccRCC were downloaded from the GEO database. Expression profiling and clinical data of ccRCC were downloaded from The Cancer Genome Atlas (TCGA) dataset. The R limma package was used to identify differentially expressed genes (DEGs). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were conducted for overlapping DEGs. Verification of mRNA expression and survival analysis in the GEPIA2 database further identified the key gene. The expression of the key gene in clinical specimens was detected by quantitative real-time PCR (qRT-PCR). Univariate and multivariate cox analysis were performed to determine whether the key gene was independent prognostic factor. Gene Set Enrichment Analysis (GSEA) was used to identify HSD11B2 related signaling pathways. The correlations between the key gene and tumor immune infiltrates were investigated via TISIDB database. **Results** A total of 20 DEGs were screened from GSE22541, GSE85258, and GSE105261 datasets. Enrichment analysis indicated that the DEGs were mainly enriched in the extracellular matrix organization, collagen-containing extracellular matrix, extracellular matrix structural constituent, and protein digestion and absorption. Verification of mRNA expression and survival analysis identified the key gene HSD11B2. qRT-PCR results showed A that HSD11B2 level was significantly down-regulated in ccRCC tissues compared with adjacent normal tissues. Multivariate Cox regression analysis showed that HSD11B2 expression was an independent prognostic factor for ccRCC patients. GSEA enrichment results showed that low expression of HSD11B2 could enrich cancer signaling pathways such as Nod-like receptor signaling pathway, cytoplasmic DNA sensing pathway and P53 signaling pathway. Immune analysis showed a significant correlation between HSD11B2 and tumor immune infiltrates in ccRCC. **Conclusions :** These findings suggest that HSD11B2 may play a key role in the metastasis of ccRCC, and HSD11B2 is correlated with prognosis and tumor immune infiltrates.

Introduction

Renal cell carcinoma (RCC) is one of the most common renal malignancies. In 2021, The United States is expected to have 76,080 new cases and 13,780 deaths through 2021[1]. Renal cell carcinoma (RCC) is one of the most deadly genitourinary tumors, with approximately 76% global 5-year survival rate[2]. ccRCC is one of the most frequent histological subtypes of RCC, accounting for 75%[3]. The main cause of death of ccRCC is tumor metastasis. Up to 30% of ccRCC patients have metastatic disease at the time of initial diagnosis[4] and about 25–40% of ccRCC patients would have metastasis after treatment[5]. In addition, patients with metastatic ccRCC are insensitive to conventional chemotherapy and radiotherapy[6]. Therefore, it is very important to explore the molecular mechanism of ccRCC metastasis.

Due to the rapid development of high-throughput sequencing technology, there have some studies on the molecular mechanism of ccRCC transfer[7, 8]. Several genetic or epigenetic alterations are thought to play an important role in the initiation and progression of ccRCC. Currently, bioinformatics methods have been used to analyze and screen candidate genes related to the prognosis and microenvironment of ccRCC[9]. For example, Ni et al[10] found that the LTF was strongly correlated with metastasis risk in ccRCC. Sun et al identified seven genes with prognostic value in ccRCC by integrated bioinformatics analysis[7]. Therefore, it is feasible to identify the biomarkers of metastatic ccRCC.

This study analyzed ccRCC mRNA expression data between tissues from metastatic ccRCC and primary ccRCC and further explore the molecular mechanisms of ccRCC metastasis. This study also implicated that HSD11B2 may be an important target for the treatment of metastatic ccRCC.

Materials And Methods

Data Collection

Gene expression profiles of GSE22541, GSE85258 and GSE105261 were download from the GEO database(<https://www.ncbi.nlm.nih.gov/geo/>)[11-13]. Expression profiling and clinical data of ccRCC were obtained from The Cancer Genome Atlas (TCGA) dataset (<https://portal.gdc.cancer.gov/>).

Identification of differentially expressed genes in GEO dataset

For each GEO dataset, differentially expressed genes(DEGs) between metastasis and non-metastasis ccRCC samples were identified with R limma package. $|\log_2\text{FoldChange}| > 1$ and $P\text{-Value} < 0.05$ were considered as threshold values for the DEGs.R ggplot2 package plotted volcano maps of DEGs in three datasets. Overlapped DEGs were drawn by R Venn Diagram package

GO and KEGG Enrichment Analysis of DEGs

The significant DEGs were enriched by Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) using R ClusterProfiler package[14]. $P\text{-value} < 0.05$ was considered as threshold values for the significant GO function and KEGG pathway.

Identification and analysis of prognostic genes in GEPIA2 database

The Gene Expression Profiling Interactive Analysis 2(GEPIA2) database (<http://gepia2.cancer-pku.cn/>) is an enhanced web server for large-scale expression profiling and interactive analysis[15]. GEPIA2 was used to identify genes that were significantly associated with overall survival(OS). Logrank p value < 0.001 was considered as statistically significant. GEPIA2 database was used to analyze the difference in expression of prognostic genes between tumor tissues and normal tissues. $|\log_2\text{FoldChange}| > 1$ and $P\text{-Value} < 0.05$ were considered as threshold values.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

15 pairs of ccRCC tissues and matched non-cancerous kidney tissues were obtained from the First Affiliated Hospital of Chongqing Medical University (Chongqing, China).All samples were pathologically confirmed and stored in liquid nitrogen (196°C)(Additional file 1: Table S1). The use of tissue was approved by the Ethics committee of the First Affiliated Hospital of Chongqing Medical University.Total RNA was extracted from ccRCC tissues and normal tissues using the Eastep® Super Total RNA Extraction Kit (Promega, Madison, WI, USA) in accordance with the manufacturer's instructions. Reverse transcription was performed using a the PrimeScript™ RT reagent Kit with gDNA Eraser (TaKaRa, Japan).qRT-PCR was carried out by using TB Green® Premix Ex Taq™ (TaKaRa, Japan) according to the manufacturer's protocol. The primers were: HSD11B2, forward,5'-CAACGCAGGCCACAATGAAG-3'and reverse 5'-ATGTGTCCATGAGTAGCGCC-3'; for GAPDH, forward 5'-GGAGTCCACTGGCGTCTTCA-3' and reverse 5'-GTCATGAGTCCTTCCACGATACC-3'. The qPCR data were analyzed by comparing $2^{-\Delta\Delta\text{CT}}$ method.

Independent prognostic analysis

To determine the correlation between clinical features and prognosis as well as the independent prognostic value of HSD11B2, univariate COX and multivariate COX analysis were performed for each variable using the R package in turn.

Establishment of prognostic nomogram

Based on the independent prognostic factors screened out by univariate and multivariate COX regression analysis, a nomogram was constructed using R "RMS" package to predict the 1-year, 3-year and 5-year survival probability of patients. Calibration was performed to evaluate the performance 1-year, 3-year and 5-year OS of the nomogram.The X-axis is the nomogram survival prediction, and the Y-axis is the observation value. The prediction capability of the nomogram will be better when the calibration curve is in accordance with the standard curve.

Gene Set Enrichment Analysis (GSEA)

GSEA analyzes gene expression profile data to understand their expression status in a specific Set of functional genes and whether such expression status is statistically significant. We used GSEA analysis to divide the groups according to the expression level of HSD11B2, and check whether there was a significant difference in survival between the two groups. Each important pathway was conducted 1000 permutations. If $FDR < 25\%$ and $NOM\ p\text{-val} < 0.05$ is considered to be significantly enriched.

TISIDB database analysis

The TISIDB database (<http://cis.hku.hk/TISIDB>) is a web portal for tumor and immune system interaction. We analyzed the correlation of HSD11B2 expression with lymphocytes and immunomodulators using TISIDB database.

Statistical analysis

R 4.1.0. (<https://www.r-project.org/>) and GraphPad Prism 8.0 were used to analyze all statistical data and graphs. Wilcoxon signed rank test and Logistic regression were used to estimate the relationship between clinicopathological parameters and HSD11B2. Univariate and multivariate Cox regression analysis was used to evaluate the relationship between HSD11B2 and OS. Forest plot was created using the “Forestplot” R package. All the statistical results of $P < 0.05$ were considered statistically significant.

Results

Identification of DEGs in GEO dataset

With $|\log_2FC| > 1$ and $P\text{-value} < 0.05$ as the critical values, 115 DEGs were identified in GSE105261, 424 DEGs in GSE22541, and 265 DEGs in GSE85258 using R limma packet (Fig. 1a-c). Detailed information for the three datasets were listed in Table 1. In addition, 20 overlapping DEGs were found in GSE105261, GSE85258 and GSE22541 datasets (Fig. 1d and Additional file 2: Table S2).

Table 1. Data set information for GSE105261, GSE22541 and GSE85258

Data Set	Platform	Sample size	Total differentially expressed genes	Up-regulated	Down-regulated
GSE85258	GPL570	Total: 29	265	183	82
		Mets: 15			
		Primary: 14			
GSE22541	GPL570	Total: 48	424	263	161
		Mets: 24			
		Primary: 24			
GSE105261	GPL10558	Total: 35	115	79	36
		Mets: 26			
		Primary: 9			

KEGG and GO Enrichment Analyses of DEGs

To understand the biological functions and pathways of overlapping DEGs, GO and KEGG analyses were performed. Gene Ontology includes biological process (BP), cellular component (CC) and molecular function (MF). The results of biological process showed that DEGs were enriched in extracellular matrix organization. The results of cell component showed that DEGs were enriched in collagen-containing extracellular matrix. The results of molecular function showed that DEGs were

enriched in extracellular matrix structural constituent (Fig. 2a and Additional file 3: Table S3). Furthermore, the result of KEGG pathway showed that DEGs were enriched in protein digestion and absorption, aldosterone-regulated sodium reabsorption, proteoglycans in cancer, ECM-receptor interaction, platelet activation, renin-angiotensin system, focal adhesion, diabetic cardiomyopathy (Fig. 2b and Additional file 3: Table S3). These results suggest that overlapping DEGs may be associated with tumor invasion and metastasis in ccRCC.

Screening and validation of the key gene

In order to further identify the key gene involved in ccRCC metastasis, survival analysis of overlapping genes was performed. The result showed that the high expression of KDELR3 (Logrank $p = 5.7 \times 10^{-7}$) and PDGFRL (Logrank $p = 8.3 \times 10^{-9}$) in ccRCC patients suggested poor prognosis. Low expression of EMX2 (Logrank $p = 5.5 \times 10^{-9}$) and HSD11B2 (Logrank $p = 4.2 \times 10^{-5}$) were associated with poor prognosis ($P < 0.001$) (Fig. 3a-3t). Meanwhile, we also used GEPIA2 database to detect mRNA expression levels of prognostic genes and found that the expression level of HSD11B2 in the primary group was higher than that in the metastatic group. (Fig. 4a-d). Therefore, these results suggest that HSD11B2 may be the key gene in the process of ccRCC metastasis.

Low expression of HSD11B2 in ccRCC and qRT-PCR validation

Firstly, we found that the expression level of HSD11B2 mRNA in ccRCC tissues was significantly lower than that in normal tissues in TCGA-KIRC dataset ($p = 3.68 \times 10^{-38}$, Fig. 5a). Then, 15 pairs of ccRCC tissues and adjacent normal kidney tissues were used to verify that HSD11B2 was significantly down-regulated in ccRCC by qRT-PCR ($p < 0.0001$) (Fig. 5b and Additional file 4: Table S4). In addition, the expression of HSD11B2 protein in normal kidney tissue and ccRCC tissue was verified using Human Protein Atlas (HPA) database. The results showed that the expression of HSD11B2 protein in tumor tissue was significantly lower than that in normal tissue (Fig. 5c).

Correlation between HSD11B2 expression level and clinical features

Through the analysis of the correlation between HSD11B2 expression level and clinical features, it was further proved that HSD11B2 is the key gene in the metastasis process of ccRCC. The association between HSD11B2 expression and clinical features in ccRCC patients is summarized in Table 2. In addition, TCGA-KIRC dataset analysis revealed significant differences in HSD11B2 among different clinical subgroups. The low expression of HSD11B2 was significantly correlated with tumor stage ($p = 6.08 \times 10^{-6}$), T stage ($p = 9.43 \times 10^{-5}$), N stage ($p = 0.0001$) and M stage ($p = 2.24 \times 10^{-5}$) (Figure 6a, b, c, d). These results suggest that HSD11B2 expression can be used as an indicator to assess the risk of metastatic renal clear cell carcinoma.

HSD11B2 expression may be an independent prognostic factor

Univariate Cox analysis showed that HSD11B2 expression was significantly correlated with OS ($p = 1.05 \times 10^{-5}$, HR = 0.801) (Fig. 7a and Table 3). Multivariate Cox analysis showed that HSD11B2 expression could be an independent prognostic factor for OS of ccRCC patients ($p = 0.009$, HR = 0.873) (Fig. 7b and Table 3).

Table 2. Univariate and multivariate analyses of HSD11B2 and clinical factors associated with OS

Parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>P</i>
Overall survival						
Age	1.03	1.02–1.04	8.50E-06	1.03	1.019–1.048	4.95E-06
Gender	1.06	0.77–1.45	0.706	1.1	0.799–1.522	0.548
T	1.92	1.63–2.27	8.61E-15	0.945	0.627–1.421	0.785
M	4.39	3.22–5.99	1.04E-20	1.54	0.796–2.968	0.200
Tumor Stage	1.89	1.66–2.16	3.98E-21	1.67	1.068–2.620	0.0245
HSD11B2	0.801	0.72–0.88	1.05E-05	0.873	0.788–0.967	0.00955

Establishment and validation of a prognostic Nomogram

Based on univariate and multivariate COX regression analysis, HSD11B2 expression, age and tumor stage can be used as independent prognostic factors to construct a Nomogram to predict 1-year, 3-year and 5-year survival(Fig.8a). The total scoreforall patients provided the estimated 1-year, 3-year and 5-year survival time. The results show that the actual OS of 1-year, 3-year and 5-yearin accord with the nomogram-predicted OS (Fig.8b).

HSD11B2 enriches multiple cancer pathways in ccRCC

GSEA analysis showed that the low expression of HSD11B2 was enriched in cancer-related pathways such as nod like receptor signaling pathway, P53 signaling pathway and cytoplasmic DNA sensing pathway. (Fig.9a-k and Additional file 5: Table S5). These results provide further evidence that low expression of HSD11B2 may contribute to the development of cancer.

Correlation between HSD11B2 expression and immune cells

In order to investigate the relationship between HSD11B2 expression and tumor immune invasion, we used the TISIDB database to analyze the correlation between HSD11B2 expression and tumor infiltrating lymphocytes (TILs) and three kinds of immunomodulators. For TILs, HSD11B2 expression was negatively correlated with most of the tumor infiltrating lymphocytes of CCRCC, such as ACT_ DC_ abundance (Spearman: $r = -0.485$, $P < 2.2e-16$), MDSC_abundance (Spearman: $r = -0.469$, $P < 2.2e-16$), Act_CD4_abundance (Spearman: $r = -0.459$, $P < 2.2e-16$), and Macrophage_abundance(Spearman: $r = -0.438$, $P < 2.2e-16$) (Figure10A). Immunomodulators include immunoinhibitors, immunostimulators and major histocompatibility complex (MHC) molecules.For immunoinhibitors, HSD11B2 expression was negatively correlated with CSF1R (Spearman: $r = -0.411$, $P < 2.2e-16$), CTLA4 (Spearman: $r = -0.366$, $P < 2.2e-16$), LGALS9(Spearman: $r = -0.346$, $P = 2.11e-16$), and BTLA (Spearman: $r = -0.341$, $P = 6.76e-16$) in ccRCC(Figure 7B).Forimmunostimulators, HSD11B2 expression was negatively correlated with TNFSF13B (Spearman: $r = -0.472$, $P < 2.2e-16$), CD86(Spearman: $r = -0.454$, $P < 2.2e-16$), TNFSF14 (Spearman: $r = -0.403$, $P < 2.2e-16$), and CD80 (Spearman: $r = -0.395$, $P < 2.2e-16$)(Figure 8A). For MHC molecules, HSD11B2 expression was negative correlated with HLA-DOB (Spearman: $r = -0.305$, $P = 8.18e-13$), HLA-DMB (Spearman: $r = -0.292$, $P = 7.83e-12$), HLA-DRA (Spearman: $r = -0.289$, $P = 1.16e-11$), and HLA-DBP1 (Spearman: $r = -0.263$, $P = 7.64e-10$) (Figure 10B).These results suggest that the expression of HSD11B2 may regulate tumor immune invasion by interacting with these immune cells.

Table 3.Association of HSD11B2 expression and the clinicopathological characters in ccRCC

Clinicopathological	Taylor cohort		
	N	mean±SD	P value
Age(years)			
≤60	259	4.82±1.67	0.5644
≥60	262	4.83±1.78	
Gende			
Female	182	5.08±1.69	0.01444
Male	339	4.69±1.73	
Tumor stage			
Stage I-II	318	5.09±1.78	5.755e-06
Stage III-IV	200	4.42±1.55	
T			
T1-T2	335	5.06±1.76	3.013e-05
T3-T4	186	4.42±1.59	
N			
N0	233	4.89±1.78	0.00130
N1	16	3.05±1.85	
M			
M0	423	4.99±1.69	5.238e-05
M1	79	4.11±1.70	

Discussion

Metastasis is the main cause of treatment failure in various cancer, including ccRCC. Although much progress has been made in metastatic ccRCC treatment, mortality and 5-year survival remain unacceptably poor[11]. Therefore, it is necessary to explore the molecular mechanism related to ccRCC metastasis and find more effective drug therapeutic targets. Previous studies have shown that the key genes controlling the pathogenesis of ccRCC include genes involved in cellular oxygen sensitivity (such as VHL), epigenetic modification (PBRM-1, SETD2, BAP1), and growth factor signal transduction (mTOR) [16]. However, previous studies on ccRCC mainly focused on finding genes differentially expressed between tumor tissues and normal tissues. In this study, we analyzed three datasets from the GEO database (GSE22541, GSE85258, and GSE105261) and identified 20 DEGs.

Then, GO and KEGG pathway enrichment analysis were performed to explore the potential biological function of DEGs. GO enrichment analysis revealed that DEGs were mainly associated with extracellular matrix organization, extracellular matrix structural constituent, and collagen trimer. The extracellular matrix (ECM) is composed of a myriad of fibrous proteins, proteoglycans, and matricellular-associated proteins[17]. ECM plays an important role in tumor development and metastasis and is also a target for cancer therapy[11, 18]. KEGG pathway analysis revealed that the DEGs were aggregated in protein digestion and absorption, proteoglycans in cancer, ECM-receptor interaction, platelet activation. All of these pathways are involved in tumor migration and invasion.[19]. In addition, platelet activation has been reported to play a role in promoting metastasis in various cancers. [20]. The above enrichment results indicated that these DEGs were closely related to tumor metastasis.

To further identify the key gene involved in the metastasis process, we performed validation of mRNA expression and survival analysis. The results show that HSD11B2 expression was down-regulated in ccRCC compared with normal tissues and was significantly associated with prognosis. In addition, qRT-PCR results also proved that the expression level of HSD11B2 was significantly down-regulated in ccRCC patients. Importantly, multivariate cox analysis demonstrated that HSD11B2 expression could be an independent prognostic factor for OS in ccRCC patients. We constructed a nomogram of ccRCC prognosis by combining HSD11B2 expression with clinical features to provide clinicians with a more effective prediction method.

Human HSD11B2 gene is located on chromosome 16q22 and consists of 5 exons with a total length of about 6kb. The gene encodes a protein containing 405 amino acids, belonging to the SDR family[21, 22]. The Results of Ming-Zhi Zhang et al demonstrated that inhibition of HSD11B2 selectively blocked the COX-2 pathway in tumors and inhibited the development of colon cancer in humans[23]. At present, some studies have proved that HSD11B2 is closely related to the proliferation and metastasis of cancer[21, 23, 24]. Combined with the above results, we inferred that HSD11B2 expression is associated with proliferation and metastasis of renal clear cell carcinoma. In addition, GSEA analysis showed that low expression of HSD11B2 is involved in tumor-related pathways and may promote tumor metastasis.

Tumor-infiltrating immune cells have become a key regulator of tumor growth and metastasis in ccRCC. TISIDB database analysis showed that HSD11B2 expression was correlated with a variety of immune cells. These results suggest that HSD11B2 plays an important role in tumor immune filtration of ccRCC.

Conclusions

In conclusion, through a series of bioinformatics analysis, this study found that the expression of HSD11B2 was associated with the metastasis and prognosis of ccRCC. HSD11B2 may be a key gene in ccRCC tumor metastasis. In addition, we also found that HSD11B2 is associated with tumor immune infiltrates of ccRCC, and may be a novel immunotherapy target of ccRCC.

Abbreviations

ccRCC: clear cell renal cell carcinoma

RCC: Renal cell carcinoma (RCC)

DEGs: Differentially expressed gene

GEO: Gene Expression Omnibus

GO: Gene Ontology

OS: Overall survival

TCGA: The Cancer Genome Atlas

KEGG: Kyoto Encyclopedia of Genes and Genomes

qRT-PCR: quantitative real-time PCR

GSEA: Gene Set Enrichment Analysis

GEPIA2: The Gene Expression Profiling Interactive Analysis 2

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article. All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LKR, HRW, and XYL designed the experimental flow. YYT and TW collect and download data. JS and SQM analyze the data. JYL and SQM wrote the manuscript. QMR revises the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Identification of the DEGs.a-c Volcano plots of DEGs in GSE105261, GSE22541 and GSE85258. d Venn diagram of the overlapping DEGs in the three GEO datasets.

a **b** **Figure 2**

GO and KEGG analysis of overlapping DEGs. aThe top 5 categories in Gene ontology. bThe significant enriched KEGG pathway terms.

Figure 3

Kaplan-Meier survival analysis of overlapping DEGs(GEPIA2 database). a-tPRRX1,EMX2,SPINK2,SFRP4,SCNN1A,COL1A1,REN,CTHRC1,HSD11B2,LUM,PTGER3,LUM,FGG,DCN,COL6A3,POSTN,KDELR3,PDGFRL, and MXR5 Kaplan-Meier curves and log-rank test results for ccRCC patients.

Figure 4

The mRNA expression levels of prognostic genes (GEPIA2 database). a-dExpression level of HSD11B2, PDGFRL, KDELR3 and EMX2 between tumor and normal kidney tissue.

Figure 5

Low expression of HSD11B2 in ccRCC .aThe expression level of HSD11B2 in ccRCC(n=532) and normal kidney tissue (n= 72) in TCGA-KIRC dataset. bqRT-PCR verified the expression level of HSD11B2 in 17 pairs of ccRCC tissues and adjacent normal kidney tissues. c Immunohistochemistry of HSD11B2 in ccRCC and normal renal tissue.

Figure 6

Correlation between HSD11B2 expression and clinicopathological features. a Tumor stages. b T stage. c N stage. d M stage.

Figure 7

HSD11B2 expression may be an independent prognostic factor. a, b Forest plot of univariate and multivariate Cox regression analysis of HSD11B2 and important clinical factors in ccRCC.

Figure 8

Establish and validate Nomogram. a A nomogram was used to predict OS of ccRCC patients, which was constructed with independent prognostic factors including Age, Tumor stage and HSD11B2. b A calibration for testing consistency between 1-year, 3-year, and 5-year OS predictions and actual results.

Figure 9

GSEA enrichment analysis diagram. aNod like receptor signaling pathway.b P53 signaling pathway. c Cytosolic DNA sensing pathway. d Leishmania infection.e Pathogenic Escherichia coli infection.f Intestinal immune network for IGA production. g Allograft rejection.h Apoptosis.i Type I diabetes mellitus.j Graft versus host disease. kPriondiseases.

Figure 10

Associations of the HSD11B2 expression level with lymphocytes and immunoinhibitors in ccRCC from TISIDB database. a Correlation between TILs abundance and HSD11B2 expression (the first four TILs with the highest correlation were plotted respectively). b Correlation between immunoinhibitors abundance and HSD11B2 expression (the first four immunoinhibitors with the highest correlation were plotted respectively).

Figure 11

Associations of the HSD11B2 expression level with immunostimulators and MHC molecules in ccRCC from TISIDB database. aCorrelation between immunostimulators and HSD11B2 expression (the first four immunostimulators with the highest correlation were plotted respectively). bCorrelation between MHC molecules and HSD11B2 expression (the first four MHC molecules with the highest correlation were plotted respectively).

Supplementary Files

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- [Additionalfile5TableS5.xlsx](#)