ISSN 2689-8268 | Volume 6

American Journal of Surgery and Clinical Case Reports

Method Article Open Access

The Low Expression of ALDOB is Associated with Poor Prognosis in Renal Clear Cell Carcinoma

Cai Z[1,2], Bai P[1], Huang H[1], Chen B[1,2], Zhang W[2], Luo Y[1], Miao C[1], Hong Y[2], Lai L[2], Zhu K[2], Zeng Y[1], Yang Y[1], Xing J[1,2], Zhuang X[1,2*] and Wang T[1*]

[1]The Key Laboratory of Urinary Tract Tumors and Calculi, Department of Urology Surgery, The First Affiliated Hospital, School of Medicine, Xiamen University, Xiamen, China

[2]The Third Clinical Medical College, Fujian Medical University, Fuzhou, China

[*]Corresponding author:

Xuan Zhuang and Tao Wang,
The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, 361003, Tel/Fax: (86)-05922137125 and (86)-05922139314;
E-mail: zhuangxuan2006@aliyun.com and taowang@xmu.edu.cn.

Received: 26 Oct 2022
Accepted: 05 Nov 2022
Published: 11 Nov 2022
J Short Name: AJSCCR

Citation:

Zhuang X and Wang T. The Low Expression of ALDOB is Associated with Poor Prognosis in Renal Clear Cell Carcinoma. Ame J Surg Clin Case Rep. 2022; 6(1): 1-11

Keywords:

ALDOB; Glycolysis; Renal clear cell carcinoma; Biomarker; Gene therapy targets

1. Abstract

1.1. Objective: Fructose bisphosphate aldolase (ALDOB) is a glycolytic metabolic enzyme, which is considered to be a therapeutic target for many cancers. However, ALDOB expression level and its regulatory mechanism in renal clear cell carcinoma is not clear. To explore ALDOB expression level and its regulatory mechanism in renal clear cell carcinoma we downloaded gene expression data sets and analyzed them by bioinformatics.

1.2. Methods: The gene expression data sets of GSE53757, GSE40435 and GSE105261 about human renal clear cell carcinoma were downloaded from the GEO database and analyzed by using the Venn diagram. We analyzed and screened out the relationship network of the interested target genes through GeneMANIA and STRING online software. These 6 target genes obtained were analyzed by Kaplan-Meier curve. GO enrichment analysis of the target gene ALDOB was performed by DAVID, and the relationship between the expression of ALDOB and immune infiltration in clear cell renal cell carcinoma was analyzed by means of TIMER and TISIDB databases. Finally, a prognostic nomogram was constructed to predict the individual's 3-year and 5-year survival probabilities.

1.3. Results: ALDOB gene is positively correlated to the survival and prognosis of patients with renal clear cell carcinoma. Furthermore, the overexpression of ALDOB can prolong the survival time of ccRCC patients. In addition, ALDOB can affect the ratio of CD4+T/CD8+T cells to influence renal clear cell carcinoma. Finally, the main mechanism of its overexpression prolonging the survival time of renal clear cell carcinoma may be involved in glycolysis.

1.4. Conclusions: These data showed that ALDOB gene could be a biomarker and therapeutic target for renal clear cell carcinoma

2. Introduction

Renal cancer, also known as renal cell carcinoma, is a tumor that originates from the renal epithelium, of which clear cell renal cell carcinoma (ccRCC) is the main type [1]. It is one of the diseases with the highest diagnosis rate in urinary system tumors. The number of diagnoses can reach 300,000 people every year, and it causes nearly 100,000 deaths [2]. It has a major impact on human health, because kidney cancer can cause fatal metastasis in the brain and lungs [3]. The 5-yr cancer-specific survival (CSS), disease-free survival (DFS) and overall survival (OS) were 97.5%, 90.9% and 95.1%, respectively [4]. Because renal cancer is not sensitive to treatments such as radiotherapy and chemotherapy, therefore surgical resection of the lesion has become a typical treatment for renal cancer. In recent years, the development of molecularly targeted drugs has provided an additional option for the treatment of renal cell carcinoma. Therefore, molecular markers (such as the expression of specific genes) can improve the accuracy of prognosis prediction [5]. The systematic identification of early diagnostic markers and prognostic molecular biomarkers will enhance the diagnosis of early renal clear cell carcinoma, thereby providing information for early and aggressive treatment.

Through databases such as TCGA, GEO, GeneMANIA, UALCAN and TIMER, we found that fructose bisphosphate aldolase

(ALDOB) is differentially expressed in clear cell renal cell carcinoma and plays important roles in the development of renal cell carcinoma. ALDOB is known for its role in metabolism and glycolysis and its main function is to catalyze the conversion of fructose-1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate [6]. Metabolomics and 13C-labeled fructose tracing studies indicate that ALDOB promotes fructose metabolism to fuel glycolysis, gluconeogenesis, and the pentose phosphate pathway [7]. It shows that ALDOB is mainly expressed in liver cancer, and the expression level in it is significantly reduced [8]. In humans, the absence of functional ALDOB enzyme due to mutations in the ALDOB gene cause hereditary fructose intolerance, characterized by metabolic disturbances [9]. Loss of hepatic ALDOB leads to a paradoxical up-regulation of glucose metabolism to favor hepatocellular carcinogenesis (HCC) [10]. It had been reported that the glycolytic enzyme ALDOB in HCC through directly binding to G6PD and inhibiting its activity, acting as a metabolic switch in glucose metabolism and regulating the metabolic reprogramming [11]. However, the role of ALDOB in ccRCC is still basically unknown. There has evidence showed that overexpression of ALDOB does not affect proliferation, but impairs the DNA matrix metalloproteinase receptor and induces apoptosis [12]. This study aims to evaluate the expression level of ALDOB in ccRCC and determine its value in predicting the survival outcome of ccRCC patients through multiple databases (including TCGA, GEO, GeneMANIA and TIMER). To further explore the possible regulatory mechanism of ALDOB in ccRCC, we used GeneMANIA, Metascape and DAVID to study the functional network involving ALDOB and the biological processes involving ALDOB interacting genes. At the same time, we assessed the expression of ALDOB in pan-carcinoma and ccRCC through the TIMER database, and further analyzed the relationship between the expression of ALDOB in clear cell renal cell carcinoma and immune infiltration. This study clarified the correlation between the expression level of ALDOB and the prognosis of ccRCC, and provided potential early diagnostic biomarkers and therapeutic targets for ccRCC.

3. Materials and Methods

Database The gene expression data set (RNA-seq) of patients with renal clear cell carcinoma (ccRCC) were download from the Cancer Genome Atlas (TCGA) project (https://portal.gdc.cancer.gov/), the GSE53757, GSE40435, GSE105261 data sets from UCSC xena browser (https://xenabrowser.net/),and the relevant survival data of ccRCC from Gene expression omnibus (https://www. ncbi. nlm.nih.gov/geo/).

Screening of key genes Download the GSE53757, GSE40435 and GSE105261 data sets related to renal clear cell carcinoma from the GEO database. We specify (FDR) < 0.05 and | log fold Change| (log FC) > 2 as differentially expressed genes, and then obtain differentially expressed genes from 3 data sets by drawing the Venn diagram. The differentially expressed genes shared by the 3 data sets are analyzed by using STRING online software, and the role relationship network of the target gene we are interested in is screened through GeneMANIA. Kaplan-Meier curve analysis of the obtained genes revealed that the high expression of ALDOB has a positive effect on the prognosis of clear cell renal cell carcinoma. We suppose that ALDOB may be a tumor suppressor gene for clear cell renal cell carcinoma.

R software 4.0.3 analysis Using R software 4.0.3 to perform ID conversion on the GSE53757 data set, based on the prognostic survival data of renal clear cell carcinoma contained in the "survival" package, a prognostic nomogram was constructed to predict the individual's 3- and 5-year survival probabilities.

GEPIA GEPIA (http://gepia.cancer-pku.cn/) uses TCGA and GTEx databases to generate gene expression profiles of multiple cancer types and normal samples. GEPIA is used to determine the effect of the expression level of ALDOB gene in ccRCC on the survival curve of patients.

GeneMANIA GeneMANIA (http://genemania.org/) is used to establish the interaction between genes. In this study, the ALDOB gene interaction network was determined by gene chip.

Metascape Metascape (http://metascape.org/gp/index.html) is an effective tool for comprehensive genomics analysis in the period of big data. It integrates functional enrichment, gene annotation and interactive group analysis. We input the differentially expressed genes into the official website to obtain the functional enrichment and gene annotation .

STRING STRING (https://www.string-db.org/) is an online database of protein interaction relationships that have been searched online. The shared differentially expressed genes were input into the official website to obtain the differentially expressed gene interaction relationships picture.

TIMER TIMER (https://cistrome.shinyapps.io/timer/) is a simple and practical cancer web server that allows users to evaluate the immunological, genomics and clinical characteristics of tumors by inputting target genes. In this study, TIMER was used to determine the expression level of ALDOB in various cancers, as well as ALDOB and B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells and evaluate the relationship between ALDOB in ccRCC and normal tissues.

TISIDB TISIDB (http://cis.hku.hk/TISIDB/) is a portal site for tumor and immune system interaction, which integrates a variety of heterogeneous data types. Use TISIDB to determine the relationship between ALDOB and B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils and dendritic cells, and ALDOB transcription expression/DNA methylation and receptors, The correlation of lymphokines, MHC molecules and chemokines.

4. Results

4.1. Screening of target genes

In the GSE53757, GSE40435 and GSE105261 data sets, we specify (FDR) < 0.05 and | log fold Change| (log FC) > 2 as differentially expressed genes, and then draw the Venn diagram to obtain 32 differentially expressed genes (Figure 1A), using STRING online software to analyze the gene interactions of 32 differential genes (Figure 1B), and use GeneMANIA to screen out the relationship network of the target genes we are interested in. Then we obtained 6 target genes include ALDOB, CLCNKB, AQP2, NPHS2, KCNJ1 and SCNN1A. Using R software to draw differential gene volcano maps for the three data sets (Figure 2). Further Kaplan-Meier curve analysis of 6 target genes showed that the high expression of ALDOB has a significant positive effect on the prognosis of clear cell renal cell carcinoma (Figure 3). Therefore, we supposed that ALDOB may be a cancer suppressor gene for clear cell renal cell carcinoma.

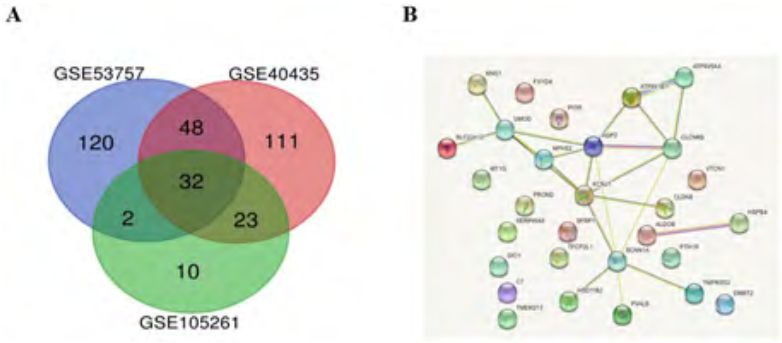


Figure 1: (A) The requirement (FDR) < 0.05 and | log2 fold Change| (log2FC) > 2 are differentially expressed genes. The differentially expressed genes of the three data sets are drawn by a Venn diagram (B) Protein-protein interaction The network consists of 25 differentially expressed proteins and is produced by the STRING online server.

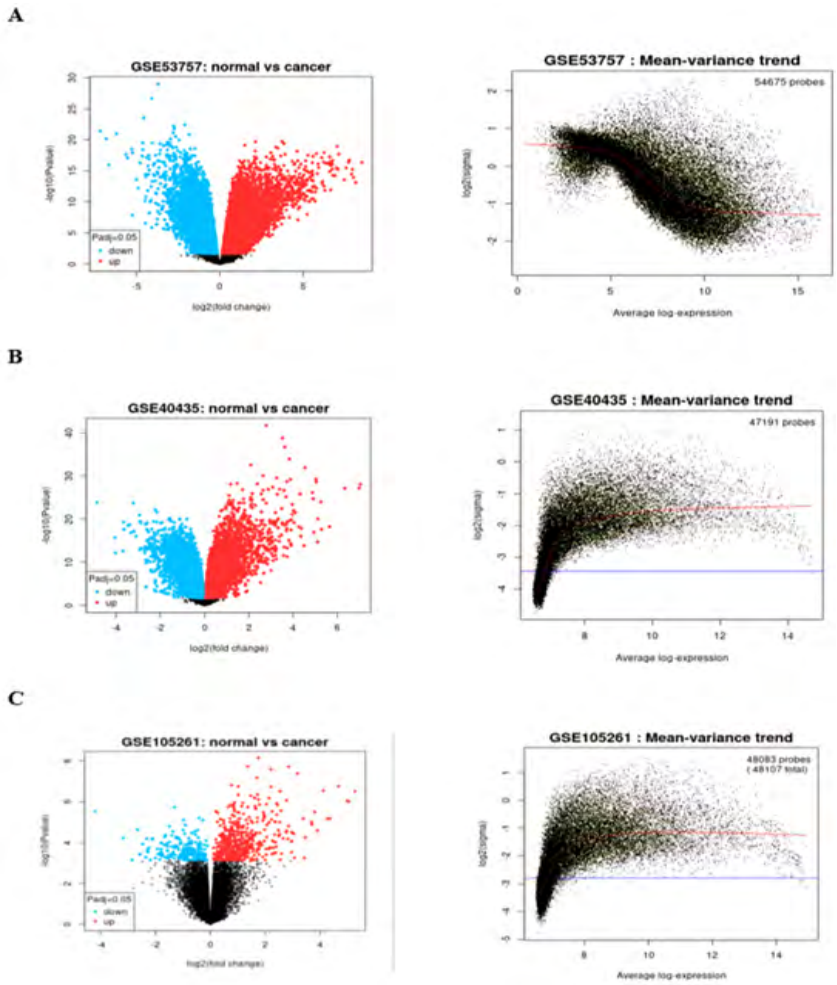


Figure 2: Gene expression of the three data sets. (A) The volcano map and mean variance trend of the up-regulated and down-regulated genes in the GSE53757 data set. (B) The volcano map and the mean variance trend of the up-regulated and down-regulated genes in the GSE40435 data set. (C) The volcano map and mean variance trend of the up-regulated and down-regulated genes in the GSE105261 data set.

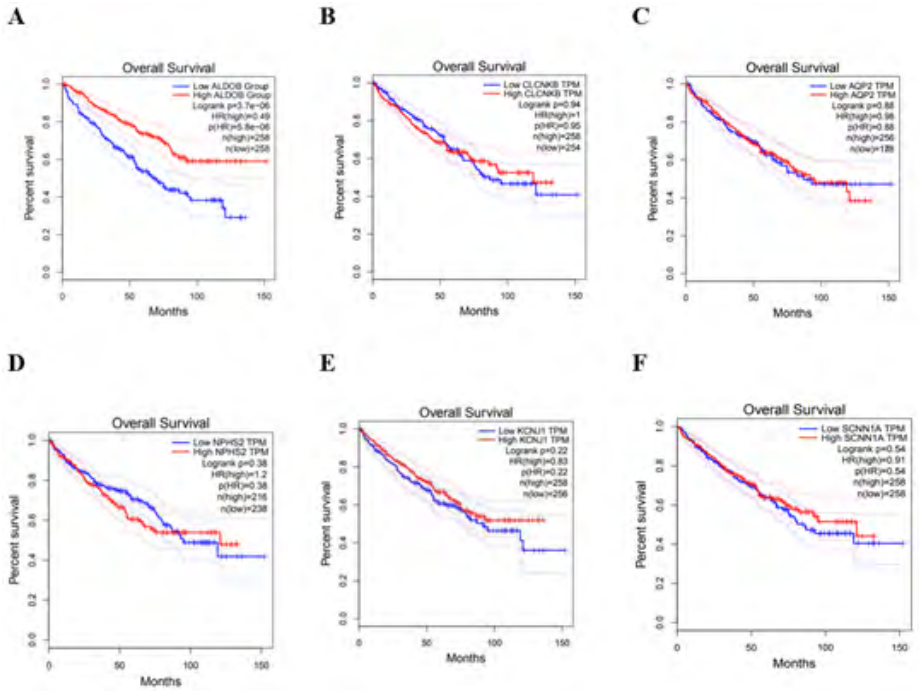


Figure 3: Using the GEPIA database to compare the effects of high and low expression levels of differentially expressed genes on the survival time of KIRC patients. (A) For ccRCC patients, elevated ALDOB expression levels are associated with longer OS results. (B) For ccRCC patients, elevated CLCNKB expression levels are associated with longer OS results. (C) For ccRCC patients, elevated AQP2 expression levels are associated with longer OS results. (D) For ccRCC patients, elevated NPHS2 expression levels are associated with shorter OS results. (E) For ccRCC patients, elevated KCNJ1 expression levels are not significantly associated with shorter OS results. (F) For ccRCC patients, elevated SCNN1A expression levels are not significantly associated with shorter OS results.

4.2. The expression of ALDOB in ccRCC and different cancers

TIMER online analysis software was used to determine the expression level of ALDOB in various cancers. Compared with normal tissues, it was found that the expression level of ALDOB increased in colon adenocarcinoma and rectal cancer, but the expression level in kidney cancer, liver cancer, gastric cancer,and pancreatic cancer was suppressed (Figure 4A). The RNA sequencing data of ALDOB was analyzed by GEPIA. Comparing each tumor tissue with the matched normal tissue, the level of ALDOB inhibition in ccRCC was also the most significant (Figure 4B). In kidney cancer, the above data shows that the expression level of ALDOB in ccRCC is significantly down-regulated. Therefore, we supposed that ALDOB acts as a tumor suppressor gene in ccRCC, and its value for the treatment and prognosis of ccRCC deserves further discussion.

4.3. Analysis of the prognostic value of ALDOB in ccRCC

We used GEPIA to analyze the shared differentially expressed genes and found that ALDOB was significantly related to the overall survival and prognosis of ccRCC. By drawing the Kaplan-Meier curve, it is found that the overexpression of ALDOB can prolong the survival time of patients compared with normal tissues. (Supplementary Figure S1A). In addition, we analyzed the survival prognosis of ALDOB in ccRCC through the UALCAN database. The result showed that the overexpression of ALDOB can also prolong the survival time of patients (Supplementary Figure S1B). The results obtained by the GEPIA and UALCAN databases are basically the same. Therefore, it can be concluded that the expression level of ALDOB has important potential prognostic value for ccRCC, and its overexpression can prolong the survival time of patients.

The overexpression of ALDOB in different grates and genders of ccRCC can prolong the survival time of patients.

In order to clarify the prognostic correlation between ALDOB and ccRCC, we used the UALCAN database to analyze the correlation between the expression level of ALDOB gene and G1, G2, G3 and G4 in ccRCC. It was found that in different grates of clear cell renal cell carcinoma, the prognosis of ccRCC patients with ALDOB overexpression was significantly better than that of patients with low expression (Supplementary Figure S1C). Further analysis of different genders showed that the prognosis of patients with high expression of ALDOB was better than that of patients with low expression (Supplementary Figure S1D). These results mean that ALDOB gene plays a role of tumor suppressor gene in ccRCC, and has great value as a potential biomarker of ccRCC.

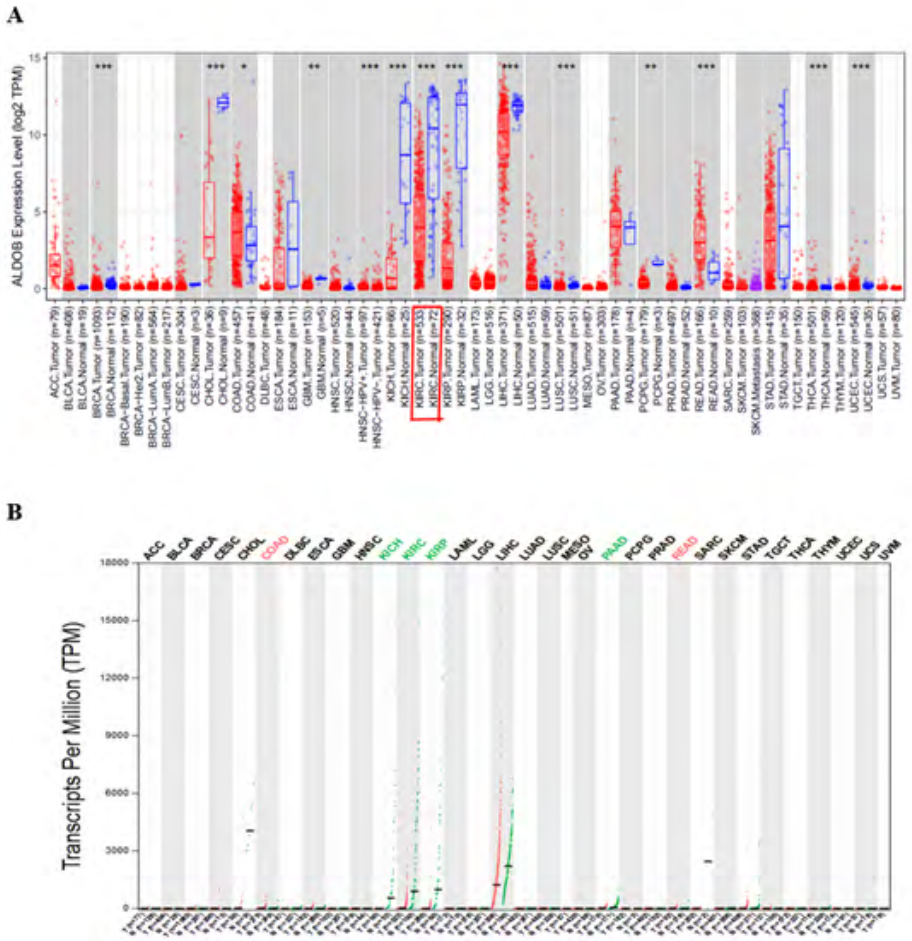
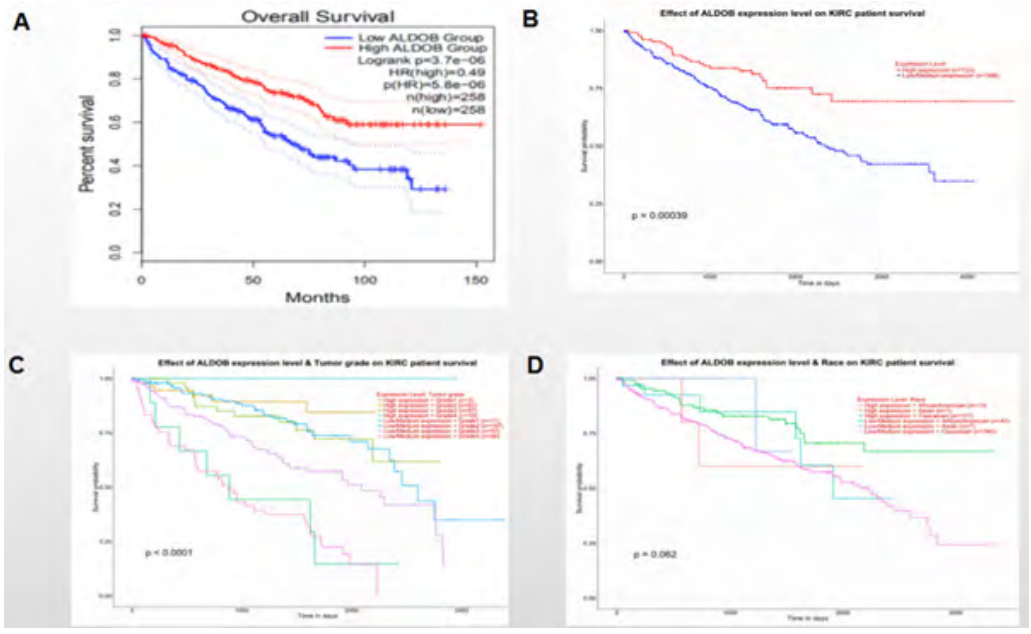


Figure 4: (A) The expression level of ALDOB gene in different cancer types compared with the corresponding normal tissues in the DriverDBV3 and TIMER databases. (B) Expression profiles of the ALDOB transcript in different cancer types and paired of normal tissues from the GEPIA database.



Supplementary Figure S1:

4.4. PPI Network of ALDOB

The functional network connection between the ALDOB gene and the relevant genes were analyzed by GeneMANIA (Figure 5). The function of ALDOB gene is mainly focused on the glycolysis process of glucose catabolism to produce pyruvate, fructose-6-benzoate, glycolysis process of glucose-6-benzoate and NADH regeneration.

4.5. Functional enrichment analysis of ALDOB

The biological process of ALDOB interacting genes was analyzed by Metascape (Figure 6A). Kidney development, multicellular homeostasis, excretion, response to xenogeneic stimuli, nephrocalcinosis, and renal insufficiency were found to be significantly regulated by these genes (Figure 6B). This means that ALDOB plays a very important role in kidney development, biological homeostasis and kidney function.

4.6. Correlation between ALDOB expression level and immune cell infiltration level in ccRCC

We used the TIMER database to visually analyze the correlation between the expression level of ALDOB and the level of immune cell infiltration in renal clear cell carcinoma, and found that the expression level of ALDOB was positively correlated with the level of infiltration of CD4+ T cells and dendritic cells. There was a weak negative correlation with the infiltration level of B cells, CD8+ T cells, macrophages and neutrophils (Figure 7A). The correlation between the expression level of ALDOB and the level of immune cell infiltration above was verified by the TISIDB database (Figure 7B-G). The level of immune cell infiltration varies with the copy number of ALDOB gene. Some immune cell infiltration levels seem to be related to changes in the copy number of the ALDOB gene, including B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Figure 7H). ALDOB transcription expression was significantly positively correlated with CCR4, CXCR1, CXCR2, and negatively correlated with CXCR4, CCR8, CXCR10, and ALDOB DNA methylation was significantly negatively correlated with most chemokines and receptors listed in TISIDB (Supplementary Figure S2).

4.7. Constructing ALDOB prognostic nomogram

We are building an ALDOB prognostic nomogram through the "survival" and "recession modeling strategy (rms)" packages of the R software, and predict the survival probability of an individual by weighing the risk score, stage, age, and gender (Figure 8).

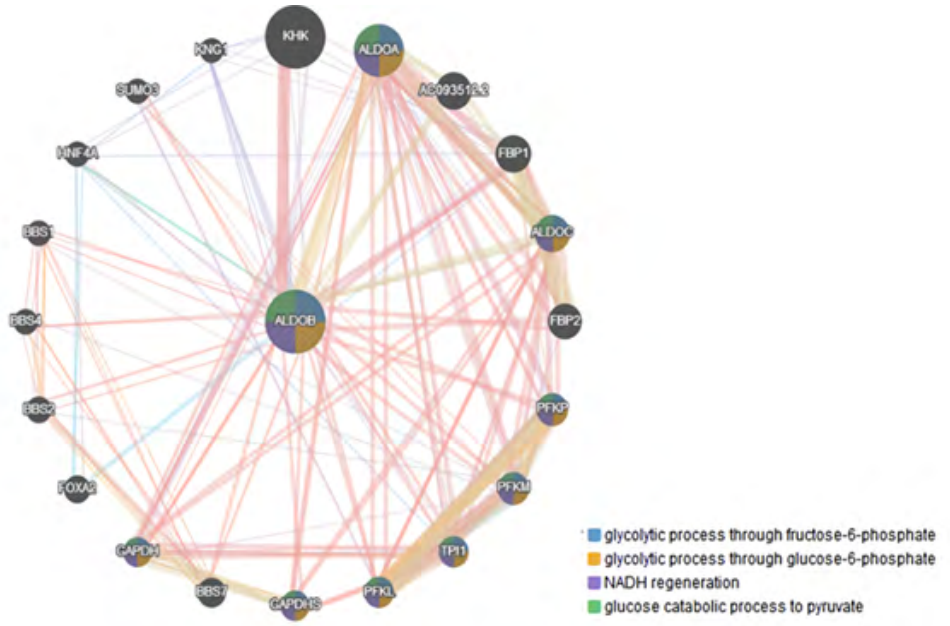


Figure 5: The PPI network of ALDOB is constructed by gene chip. PPI: protein-protein interaction.

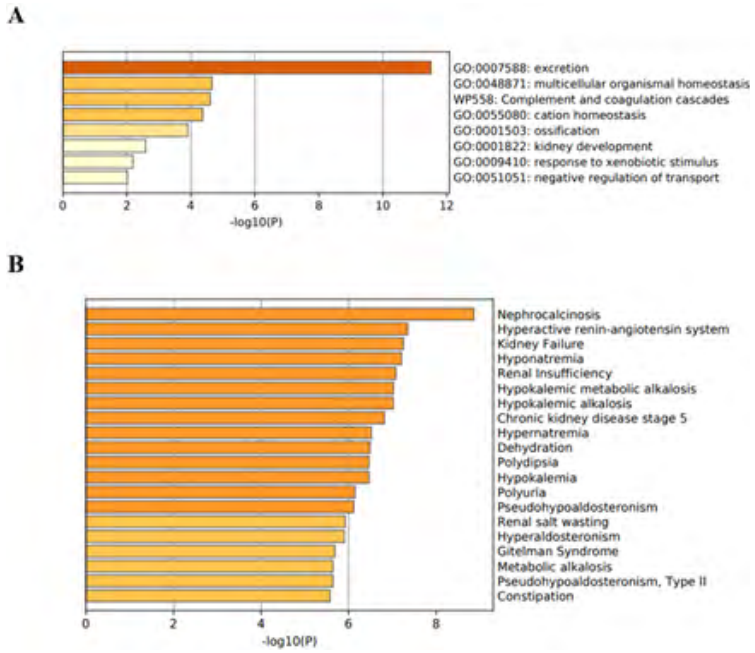
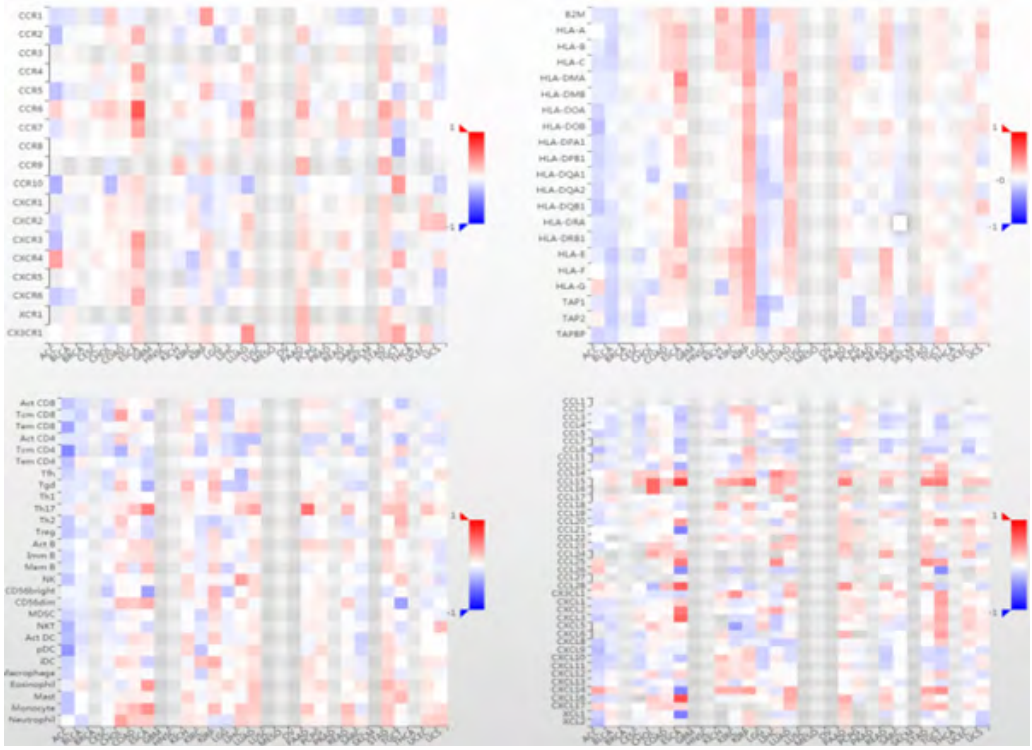


Figure 6: Biological processes involved in ALDOB interaction genes. (A) A heat map from Metascape, showing the main biological processes involving ALDOB interacting genes. (B) Heat map from Metascape, showing the function of proteins involved in ALDOB interacting genes.



Supplementary Figure S2:

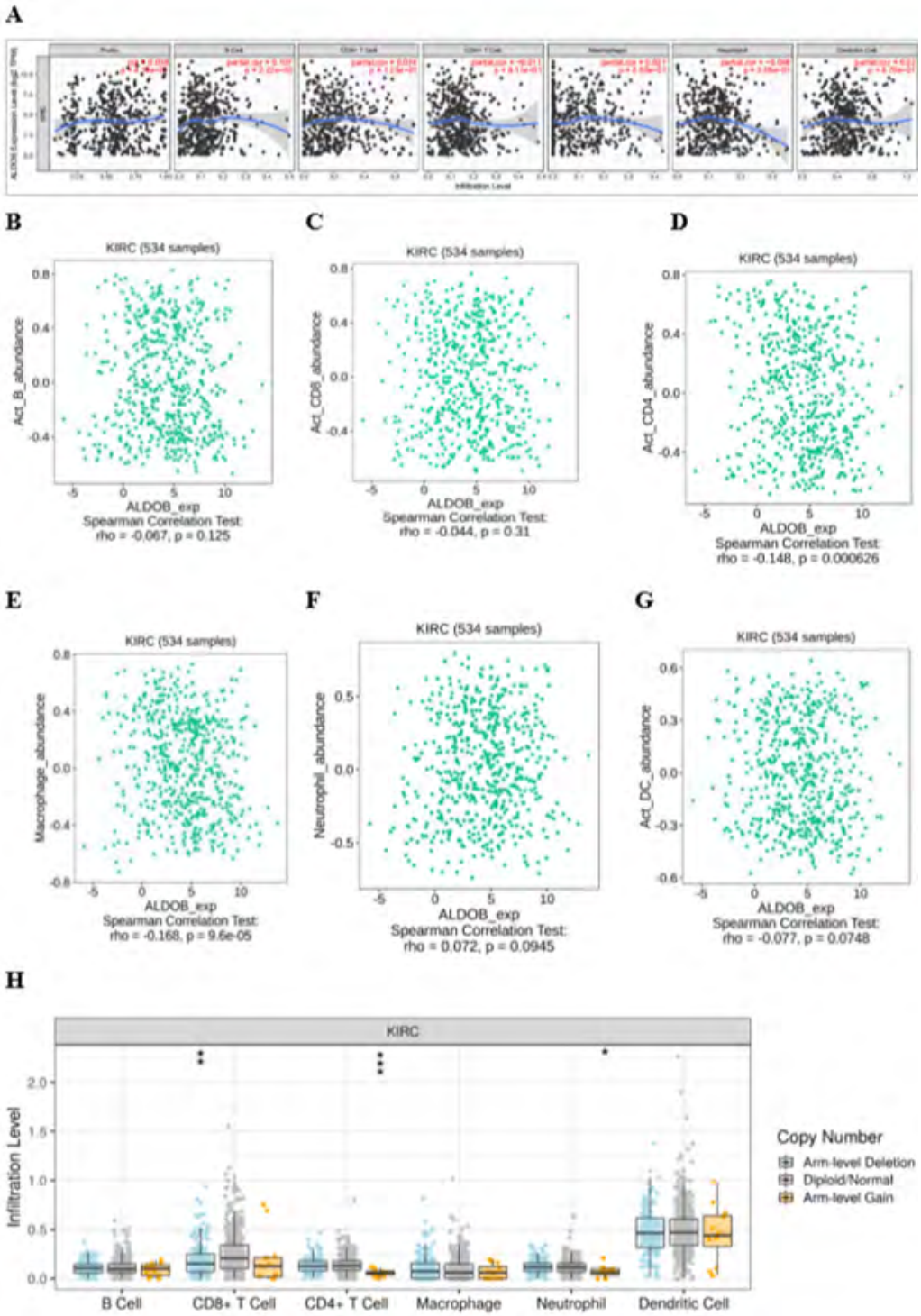


Figure 7 (A): TIMER database: the relationship between the expression level of ALDOB and the level of immune cell infiltration in ccRCC population. (B-D) TISIDB database: The relationship between the expression level of ALDOB and the level of immune cell infiltration in ccRCC population. (G) The relationship between the copy number of ALDOB gene and the level of immune cell infiltration. The relationship between the copy number of ALDOB in ccRCC and the level of immune cell infiltration.

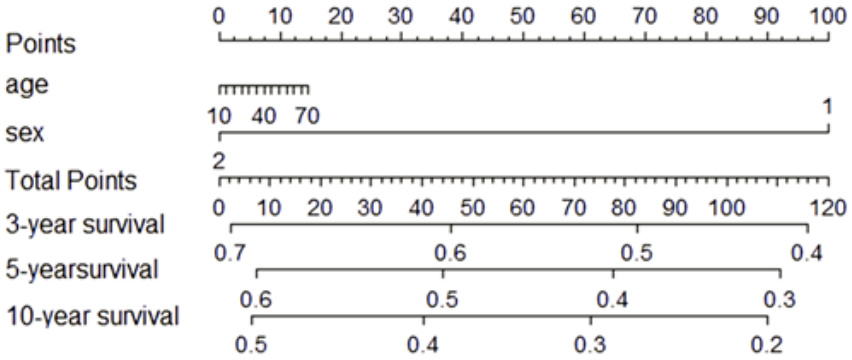


Figure 8: The nomogram of the gene signature and its performance in the training set and internal and external validation sets. The predictive model was presented with a nomogram.

5. Discussion

Renal cell carcinoma is one of the malignant tumors with the highest incidence in the world [12], and it is also one of the 3% cancers with the highest incidence in Western countries [13]. In the past two decades, the mortality rate of renal cell carcinoma in the world has increased by 2% every year [3]. The main pathological type of renal cell carcinoma is renal clear cell carcinoma, which is named due to its microscopic characteristics of clear cytoplasm, The prognosis of ccRCC is worse than that of chromophobe cell carcinoma, and it is harmful to humans [14, 15]. Due to the lack of effective biomarkers, many patients have been diagnosed in the middle and advanced stage [16]. At present, the main treatment for renal clear cell carcinoma is surgery [17]. With the research of targeted drugs, the research on ideal targets has also been intensified. The so-called ideal targets have high specificity and attack tumor cells without harming normal tissues. Therefore, it is particularly important to explore biomarkers for early diagnosis and target therapy of ccRCC.

Aldolase family members are the fourth enzyme in the glycolysis process. They include ALDOA, ALDOB, and ALDOC. There are three different genes that encode aldolase A, B, and C, and these three isoenzymes are expressed in the specific human organs [18]. ALDOA is expressed in embryos and is abundantly available in adult muscle tissue [19, 20]. ALDOB is a glycolytic metabolic enzyme, mainly expressed in the gastrointestinal tract, liver and kidney [21]. ALDOC, the third type of aldolase, is abundant in the central nervous system, including in Purkinje cells of the cerebrum, hippocampus and in Schwann cells [22, 23]. Cancer originates from imbalances between DNA damage and DNA repair [24]. Studies have found that ALDOB not only regulates glycolysis, but also plays a regulatory role by participating in the regulation of DNA damage repair [25]. Increased glycolysis, a hallmark of malignant cancers,correlates with invasive potential and poor prognosis. As we know,ALDOB is an important glycolytic enzymes. In renal cell carcinoma, the downregulation of ALDOB can maintain high levels of fructose 1,6-bisphosphate (FBP) which were required for cancer growth because of its ability to affect the redox status [26]. Therefore, we consider whether the low expression of ALDOB portended significantly worse disease-free survival and overall survival in ccRCC patients.

Therefore, in this study, we used various databases, including TCGA, GEO, GeneMANIA, and TIMER, to explore the correlation between ALDOB expression and ccRCC. Through these databases, we found that the expression of ALDOB in renal cell carcinoma was significantly lower than the expression in normal tissues, but the effect of its low expression on ccRCC is still unclear. Then, we used the GEPIA database to analyze the impact of ALDOB expression on the survival time of ccRCC, and found that the overexpression of ALDOB can prolong the survival time of ccRCC patients. Then we used the UALCAN database to verify that the results were consistent. These results showed that ALDOB can be used as an important prognostic indicator for ccRCC patients. In addition, we utilized the UALCAN database to analyze the correlation between the expression level of ALDOB gene and different grates in ccRCC. It was found that in G1, G2, G3, and G4 of clear cell renal cell carcinoma, the prognosis of ccRCC patients with overexpression of ALDOB was significantly better than that of patients with low expression. Further analysis of gender showed that patients with high expression had better prognosis than those with low expression. The above results all indicate that ALDOB can be used as a prognostic biomarker for ccRCC.

The interaction between tumor cells and the tumor microenvironment (TME) plays a key role in tumorigenesis, progression, metastasis, and drug resistance [27, 28]. Various cellular phenomena such as alterations in the tumor microenvironment, inflammation, oxidative stress, and hypoxia promote tumor initiation, progression, and metastasis [29]. Dendritic cells are antigen-presenting cells that have specific roles in initiating and regulating immunity [30, 31], and can activate CD4+ T cells and CD8+ T cells. The ratio of CD4+ T/CD8+ T cells can directly reflect the cellular immune function of the body. The decreased ratio of CD4+ T/CD8+ T cells is mainly seen in immunodeficiency and malignant tumors. In this study, we found that the expression level of ALDOB was positively correlated with the infiltration levels of CD4+ T cells and dendritic cells, and was weakly correlated with the infiltration levels of B cells, CD8+ T cells, macrophages and neutrophils neg-

ative correlation. However, ALDOB is in a state of low expression in ccRCC, resulting in a decrease in the expression level of CD4+ T cells, which in turn leads to a decrease in the ratio of CD4+ T/CD8+ T cells. From the perspective of immunity, it is further clarified that the low expression of ALDOB in ccRCC has an adverse effect on its prognosis.

Some studies have found that MYC is the nuclear protein carcinoid gene, including four types of c-MYC, n-MYC, l-MYC and r-MYC. It is a transcription factor with a wide range of functions. Regulates cell differentiation and proliferation. MYC overexpression leads to the progression and metastasis of multiple cancer types including prostate cancer [32-37], and MYC gene knockout can significantly inhibit prostate cancer metastasis [38-40]. However, the c-MYC proto-oncogene is one of the most activated genes, which can transcribe ALDOB, and its transcription level is regulated by Set7/9. Set7/9 is a lysine-specific methyl-transferase that regulates histone and non-histone substrates, thereby positively regulating the transcription level of c-MYC. Therefore, the role of c-MYC in renal clear cell carcinoma needs further study.

6. Conclusions

We used a variety of databases to find that the expression level of ALDOB in ccRCC was suppressed. Through survival analysis of the effect of ALDOB expression on the survival time of ccRCC, we found that overexpression of ALDOB can significantly prolong the survival time of ccRCC patients. The above results show that ALDOB is an important renal cancer biomarker and a potential high-specific therapeutic target. The main mechanism of its overexpression prolonging the survival time of renal clear cell carcinoma may be involved in glycolysis, but more studies are needed to confirm our findings and promote the clinical application of ALDOB as a prognostic marker or therapeutic target of ccRCC.

7. Grant Support

This study was funded by Xiamen science and technology plan (#3502Z20194006), Natural Science Foundation of Fujian Province (#2020J05304 and #2021J011346) and Young and Middle-aged Backbone Foundation of the Fujian Provincial Health and Family Planning Commission (#2019-ZQNB-26).

References

1. Sánchez-Gastaldo A, Kempf E, Alba AGD, Duran I, Systemic treatment of renal cell cancer: A comprehensive review. 2017; 60: 77-89.
2. Ricketts C, Crooks D, Linehan WM. Targeting HIF2α in Clear-Cell Renal Cell Carcinoma. 2016; 30: 515-517.
3. Xu J, Liu Y, Liu J, Shou Y, Xiong Z, Xiong H, et al. Low Expression Levels of SLC22A12 Indicates a Poor Prognosis and Progresses Clear Cell Renal Cell Carcinoma. 2021; 11: 659208.
4. Vartolomei M, Matei DV, Renne G, Tringali VM, Crisan N, Musi G, et al. Robot-assisted Partial Nephrectomy: 5-yr Oncological Outcomes at a Single European Tertiary Cancer Center. 2017; S2405456917302420.
5. Tamayo P, Cho Y, Tsherniak A, Greulich H, Ambrogio L, Schouten-van Meeteren N, et al. Predicting relapse in patients with medulloblastoma by integrating evidence from clinical and genomic features. 2011; 29: 1415-23.
6. He J, Jin Y, Chen Y, Yao H, Xia Y, Ma Y, et al. Downregulation of ALDOB is associated with poor prognosis of patients with gastric cancer. 2016; 9: 6099-6109.
7. Bu P, Chen K, Xiang K, Johnson C, Crown S, Rakhilin N, et al. Aldolase B-Mediated Fructose Metabolism Drives Metabolic Reprogramming of Colon Cancer Liver Metastasis. 2018; 27: 1249-62.
8. Asaka M, Kimura T, Meguro T, Kato M, Kudo M, Miyazaki T, et al. Alteration of aldolase isozymes in serum and tissues of patients with cancer and other diseases. 1994; 8: 144-8.
9. Giwercman A, Sahlin K, Parada IP, Pawlowski K, Fehninger C, Giwercman YL, et al. Novel protein markers of androgen activity in humans: proteomic study of plasma from young chemically castrated men. 2022; 11.
10. He X, Li M, Yu H, Liu G, Wang N, Yin C, et al. Loss of hepatic aldolase B activates Akt and promotes hepatocellular carcinogenesis by destabilizing the Aldob/Akt/PP2A protein complex. 2020; 18: e3000803.
11. Li M, He X, Guo W, Yu H, Zhang S, Wang N, et al. Aldolase B suppresses hepatocellular carcinogenesis by inhibiting G6PD and pentose phosphate pathways. 2020; 1: 735-747.
12. Klümper N, Ralser D, Bawden E, Landsberg J, Zarbl R, Kristiansen G, et al. LAG3 (,) DNA methylation correlates with LAG3 expression by tumor and immune cells, immune cell infiltration, and overall survival in clear cell renal cell carcinoma. 2020; 8.
13. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh J, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. 2013; 49: 1374-403.
14. Capitanio U, Cloutier V, Zini L, Isbarn H, Jeldres C, Shariat S, et al. A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. 2009; 103: 1496-500.
15. Keegan K, Schupp C, Chamie K, Hellenthal N, Evans C, et al. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. 2012; 188: 391-7.
16. Siegel R, Miller K, Jemal A. Cancer statistics. 2018; 68(2018): 7-30.
17. Zini L, Perrotte P, Jeldres C, Capitanio U, Duclos A, Jolivet-Tremblay M, et al. A population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses. 2009; 103: 899-904.
18. Chang Y, Yang Y, Tien C, Yang C, Hsiao M. Roles of Aldolase Family Genes in Human Cancers and Diseases. 2018; 29: 549-559.
19. Mamczur P, Dzugaj D. Aldolase A is present in smooth muscle cell nuclei. 2008; 55: 799-805.
20. Yao D, Tolan D, Murray M, Harris D, Darras B, Geva A, et al. Hemolytic anemia and severe rhabdomyolysis caused by compound heterozygous mutations of the gene for erythrocyte/muscle

isozyme of aldolase, ALDOA(Arg303X/Cys338Tyr). 2004; 103: 2401-3.

21. Mukai T, Joh K, Arai Y, Yatsuki H, Hori K. Tissue-specific expression of rat aldolase A mRNAs. Three molecular species differing only in the 5'-terminal sequences. 1986; 261: 3347-54.
22. Fujita H, Aoki H, Ajioka I, Yamazaki M, Abe M, Oh-Nishi A, et al. Detailed expression pattern of aldolase C (Aldoc) in the cerebellum, retina and other areas of the CNS studied in Aldoc-Venus knock-in mice. 2014; 9: e86679.
23. Zahid S, Khan R, Oellerich M, Ahmed N, Asif AR. Differential S-nitrosylation of proteins in Alzheimer's disease. 2014; 256: 126-36.
24. Sandovici I, Buhuşi M, Stoica O, Covic M. [DNA repair pathways and their involvement in human diseases]. 2002; 107: 247-57.
25. Lian J, Xia L, Chen Y, Zheng J, Ma K, Luo L, et al. Aldolase B impairs DNA mismatch repair and induces apoptosis in colon adenocarcinoma. 2019; 215: 152597.
26. Wang J, Wu Q, Qiu J. Accumulation of fructose 1,6-bisphosphate protects clear cell renal cell carcinoma from oxidative stress. 2019; 99: 898-908.
27. Argentiero, De Summa S, Di Fonte R, Iacobazzi R, Porcelli L, et al. Gene Expression Comparison between the Lymph Node-Positive and -Negative Reveals a Peculiar Immune Microenvironment Signature and a Theranostic Role for WNT Targeting in Pancreatic Ductal Adenocarcinoma: A Pilot Study. 2019; 11.
28. Del Prete A, Schioppa T, Tiberio L, Stabile H, Sozzani S. Leukocyte trafficking in tumor microenvironment. 2017; 35: 40-47.
29. Bishayee B. The role of inflammation and liver cancer. 2014; 816: 401.
30. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. 1998; 392: 245-52.
31. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. 2001; 106: 255-8.
32. Rapp U, Korn C, Ceteci F, Karreman C, Luetkenhaus K, Serafin V, et al. MYC is a metastasis gene for non-small-cell lung cancer. 2009; 4: e6029.
33. Lin X, Sun R, Zhao X, Zhu D, Zhao X, Gu Q, et al. C-myc overexpression drives melanoma metastasis by promoting vasculogenic mimicry via c-myc/snail/Bax signaling. 2017; 95: 53-67.
34. Klotz R, Thomas A, Teng T, Han SM, Iriondo O, Li L, et al. Circulating tumor cells exhibit metastatic tropism and reveal brain metastasis drivers. Cancer Discov. 2020; 10: 86-103.
35. Hubbard GK, Mutton LN, Khalili M, McMullin RP, Hicks JL, Bianchi-Frias D, et al. Combined myc activation and pten loss are sufficient to create genomic instability and lethal metastatic prostate cancer. Cancer Res. 2016; 76:283-92.
36. Nowak DG, Cho H, Herzka T, Watrud K, DeMarco DV, Wang VM, et al. Myc drives pten/trp53-deficient proliferation and metastasis due to il6 secretion and akt suppression via phlpp2. Cancer Discov. 2015; 5:636-51.
37. Cho H, Herzka T, Zheng W, Qi J, Wilkinson JE, Bradner JE, et al. Rapidcap, a novel gem model for metastatic prostate cancer analysis and therapy, reveals myc as a driver of pten-mutant metastasis. Cancer Discov. 2014; 4:318-33.
38. Lee HY, Cha J, Kim SK, Park JH, Song KH, Kim P, et al. C-myc drives breast cancer metastasis to the brain, but promotes synthetic lethality with trail. Mol Cancer Res. 2019; 17:544-554.
39. Chu GC, Zhau HE, Wang R, Rogatko A, Feng X, Zayzafoon M, et al. Rank- and c-met-mediated signal network promotes prostate cancer metastatic colonization. Endocr Relat Cancer. 2014; 21:311-26.
40. Arriaga JM, Panja S, Alshalalfa M, Zhao J, Zou M, Giacobbe A, et al. A MYC and RAS co-activation signature in localized prostate cancer drives bone metastasis and castration resistance. Nat Cancer 2020; 1:1082-1096.