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PGGHG and ODF3B as New Tumor Suppressor Genes in Renal Cell Carcinoma

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Abstract

Background: Renal cell carcinoma (RCC) is the most frequent heterogeneous type of kidney cancer. Although the role of many genes in the development of RCC has been shown, its specific molecular mechanism is still unknown.

Objective: In this research, we studied the expression profile of two uncharacterized genes, *PGGHG* and *ODF3B*, with possible role in renal cancers in our RCC patients.

Method: Using TCGA data, firstly, we looked for significant downregulated genes in RCC with poor overall survival (OS) time. Then, we only considered two uncharacterized genes with involvement in the same protein network in this cancer including *ODF3B* and *PGGHG*. Their expression was determined using the QPCR in our 40 RCC patients. Moreover, Enrichr was used to investigate their pathways, ontologies, and possible upstream transcription factors.

Result: In contract to TCGA, our study revealed the low expression of *PGGHG* and *ODF3B* in our KIRC patients. The expression level of *ODF3B* in the patients who had tumor size > 4cm was significant. Our data found the possible upstream transcription factor of *ODF3B* and *PGGHG* regulating their expression in biological pathways, mainly PPARG as the same upstream transcription factor affecting both genes.

Conclusion: Since our study showed lower expression of these genes in our patients in contrast to TCGA data, more studies from different population with higher number of patients are needed to find whether different population and statuses are involved in this reverse result and also to determine the precise mechanism of their involvement in RCC pathogenesis.

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Keywords: Carcinoma, ODF3B, PGGHG, Renal Cell.

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney malignancies and highly aggressive heterogeneous disease [1,2]. The most common histological subtypes of RCC are clear cell, papillary, and chromophobe responsible for 70%, 10–15%, and 5% of the RCC types, respectively [3,4]. So far, many factors have been implicated in the development of ccRCC, including genetic and environmental factors. Moreover, dysregulation of several genes has been contributed to the RCC progression and metastasis in different pathways. Clear cell RCC patients respond poorly to radiotherapy and chemotherapy. Therefore, the molecular predictions of disease progression and metastasis are important for therapies. We are looking to explore new molecular biomarkers of disease progression and ccRCC-specific molecular mechanisms that may provide new targeted treatment options.

TCGA data from GDC Data Portal (https://portal.gdc.cancer.gov) contains a huge genomic, epigenomic, transcriptomic, and proteomic data of numerous cancer types which can help scientists to use its data for investigation of uncharacterized genes in cancers. Using analysis of TCGA renal cancers data, we found altered expression of two uncharacterized genes, including protein-glucosylgalactosylhydroxylysine glucosidase *(PGGHG)* (also known as *ATHL1*) and outer the dense fiber of sperm tails 3B *(ODF3B*) (Also known as *FAP123*; *ODF3L3*) in KIRC. Their altered expression was correlated with worse prognosis with reduced survival in the KIRC patients. Moreover, using STRING database we found their involvement in the same network. Therefore, our study set out to investigate the potential contribution of these two genes with unknown roles, in RCC pathogenesis.

The chromosomal positions of *ODF3B* is 22q13.33. The pronephros is consisted of two types of epithelial cells, including transportive and multiciliated cells (MCCs). The epithelial MCCs expresses ODF3B protein [5]. Previous study showed that *ODF3B* transcripts localize in pronephros cells and labels maturing MCCs in renal progenitors [6].

In relation to the *PGGHG (*located on 11p15.5*)*, it was found to act in release of glucose from human placental type IV collagen [7]. Data extracted from Enrichr (https://maayanlab.cloud/Enrichr/) shows its involvement in hydrolase activity, hydrolyzing O-glycosyl compounds (GO: 0004553). Moreover, previous study conducted by Wei Shi et al. showed higher expression of hsa-mir-484 correlated with worse prognosis in breast cancer. In their study, they found that one of target gene of hsa-mir-484 was PGGHG [8]. Based on these evidence, identification of the role of these two genes in renal cancer may help find new pathways in this cancer.

Materials and MAethods

Gene selection

Using UALCAN webserver (http://ualcan.path.uab.edu.), firstly, we looked for significant upregulated genes in TCGA-KIRC. Next, we looked for genes with poor overall survival (OS) time with worse prognosis among them, and then we only considered two uncharacterized genes in KIRC including *ODF3B* and *PGGHG*. Moreover, we investigated the expression of these genes in other two types of renal cancer including Kidney renal papillary cell carcinoma (KIRP) and Kidney chromophobe (KICH). In addition to these data, to strengthen their role in renal cancers, we looked for their protein network using STRING (https://string-db.org) to find whether they are connected in same protein network and also to help identify their possible pathways.

Patient characteristics and tumor samples

To investigate mRNA expression of *PGGHG* and *ODF3B* in renal cancers, we collected 40 tumor tissues and their adjacent normal tissues of RCC patients from Ali-Asghar, Namazi, and Ghadir Mother and Child Hospitals (Shiraz, Iran). In total, RCC patients had not received radiotherapy and chemotherapy before surgery. The samples were immediately immersed in liquid nitrogen and stored at -80°C until use. The clinicopathologic and demographic features of RCC patients are shown in Table 1. After surgery, we followed up patients to find they had all-cause mortality.

RNA extraction and cDNA synthesis

Using the Trizol isolation reagent (Invitrogen, Thermo Fisher) total RNA was extracted from each sample according to the manufacturer's instructions. Gel electrophoresis and a nanodrop spectrophotometer (BioTek, HTX multi-mode reader) was used to assess RNA quality and quantity, respectively. Total RNA was reverse-transcribed into first-strand cDNA using the PrimeScript™ RT Reagent Kit (Takara, Cat.No: RR037A).

qRT-PCR

QRT-PCR was carried out using Power SYBR® Green PCR Master Mix (ABI, USA) on the 7500 real-time PCR system (ABI, life technology). 7.5 µl BioFACT™ master mix including SYBR Green (Ampliqon, Cat.No: A325402-25), along with 1 µl of cDNA, 0.75 µl of each primer and 5 µl DNase-free dH_2O was used for total volume of 15 µl reaction mix. B2M was used as an internal control. The sequences for primers are shown in Supplementary Table 1. Relative quantification was calculated by the $2^{-\Delta\Delta CT}$.

Enrichment analysis

In our study we also used Enrichr database (https://maayanlab.cloud/Enrichr/) to look for their pathways, ontologies, and possible upstream transcription factors and among others. To evaluate survival analysis our patients, we used the Kaplan–Meier method based on observed survival times. This analysis was performed using IBM SPSS version 26 software (IBM Corp, Armonk, NY).

Statistical analysis

Statistical analyses were done in IBM SPSS version 26 software (IBM Corp, Armonk, NY). The data were presented as mean and standard deviation for ΔΔCt, or median for fold change. Wilcoxon test was used to compare fold changes between tumors and adjacent normal renal

		ODF3B level					PGGHG level				
		N	Mean	SD	Median	P-value	N	Mean	SD	Median	P-value
Sex	male	29	0.924	0.984	0.620	0.844	29	0.795	1.037	0.309	0.296
	female	11	0.748	0.637	0.660		11	0.971	0.857	0.798	
Tumor size	≤4	20	1.054	0.881	0.919	**0.060**	20	0.758	0.843	0.540	0.745
	>4	20	0.697	0.899	0.357		20	0.928	1.122	0.333	
Tumor focality	focal	25	1.097	1.031	0.774	0.067	25	0.840	1.039	0.491	0.856
	unifocal	15	0.507	0.434	0.587		15	0.849	0.918	0.309	
Tumor type	clear cell	27	0.959	0.835	0.688	**0.004**	27	0.925	0.934	0.505	**0.017**
	papillary	5	1.283	1.330	0.774		5	0.974	0.958	0.644	
	chromophore	6	0.043	0.030	0.031		6	0.069	0.096	0.029	
	oncocytoma	2	1.231	0.864	1.231		2	1.730	2.427	1.730	
Tumor necrosis	seen	20	0.924	1.086	0.601	0.715	20	0.598	0.771	0.331	0.160
	not seen	20	0.827	0.685	0.674		20	1.088	1.124	0.635	
Fuhrman nuclear grade	1	5	0.328	0.308	0.233	0.113	5	0.359	0.573	0.090	0.225
	2	21	0.768	0.920	0.470		21	0.818	0.961	0.399	
	3	9	1.189	0.711	1.603		9	1.268	1.180	0.798	
	4	5	1.310	1.271	1.065		5	0.665	0.979	0.302	
Lymph vascular perineural invasion	No	8	1.057	1.055	0.841	0.467	8	0.801	1.042	0.304	0.866
	Yes	32	0.830	0.866	0.625		32	0.854	0.985	0.445	
Extension	No	30	0.870	0.884	0.625	1.000	30	0.901	1.046	0.445	0.779
	Yes	10	0.892	0.985	0.695		10	0.670	0.787	0.330	
Cancer history	No	19	0.891	0.998	0.587	0.882	19	0.897	1.085	0.399	0.903
	Yes	21	0.861	0.820	0.774		21	0.794	0.906	0.333	
BMI	≤25	9	1.224	1.433	0.616	0.918	9	0.762	0.928	0.234	0.784
	25-29	26	0.771	0.689	0.645		26	0.826	1.007	0.445	
	≥30	5	0.791	0.650	0.620		5	1.080	1.134	0.798	
Kidney disease	No	29	0.867	0.838	0.629	0.880	29	0.880	1.038	0.357	0.940
	Yes	11	0.897	1.083	0.470		11	0.745	0.860	0.399	

Table 1. The association of *ODF3B* and *PGGHG* expression levels with demographic and clinicopathological factors in RCC patients.

		ODF3B level					PGGHG level				
		Low		High		P-value	Low		High		P-value
		N	%	N	%		N	%	N	%	
Tumor size	≤4	6	30.0%	14	70.0%	**0.011**	9	45.0%	11	55.0%	0.527
	>4	14	70.0%	6	30.0%		11	55.0%	9	45.0%	
Tumor focality	focal	11	44.0%	14	56.0%	0.327	12	48.0%	13	52.0%	0.744
	unifocal	9	60.0%	6	40.0%		8	53.3%	7	46.7%	
Fuhrman nuclear grade	1	4	80.0%	1	20.0%	0.157	4	80.0%	1	20.0%	0.093
	2	12	57.1%	9	42.9%		10	47.6%	11	52.4%	
	3	2	22.2%	7	77.8%		2	22.2%	7	77.8%	
	4	2	40.0%	3	60.0%		4	80.0%	1	20.0%	
Lymph vascular perineural invasion	No	4	50.0%	4	50.0%	1.000	5	62.5%	3	37.5%	0.429
	Yes	16	50.0%	16	50.0%		15	46.9%	17	53.1%	
BMI	≤25	5	55.6%	4	44.4%	0.793	6	66.7%	3	33.3%	0.508
	25-29	12	46.2%	14	53.8%		12	46.2%	14	53.8%	
	≥30	3	60.0%	2	40.0%		2	40.0%	3	60.0%	

Background disease	None	11	52.4%	10	47.6%	0.727	12	57.1%	9	42.9%	0.313
	High blood pressure	7	58.3%	5	41.7%		6	50.0%	6	50.0%	
	diabetes	1	33.3%	2	66.7%		1	33.3%	2	66.7%	
	High blood pressure and diabetes	1	33.3%	2	66.7%		0	0.0%	3	100.0%	
	prostate problems	0	0.0%	1	100.0%		1	100.0%	0	0.0%	
Kidney disease	No	14	48.3%	15	51.7%	0.723	15	51.7%	14	48.3%	0.723
	Yes	6	54.5%	5	45.5%		5	45.5%	6	54.5%	
Kidney stone	No	10	47.6%	11	52.4%	0.752	10	47.6%	11	52.4%	0.752
	Yes	10	52.6%	9	47.4%		10	52.6%	9	47.4%	

Table 2. The association of *ODF3B* and *PGGHG* expression levels with demographic and clinicopathological factors in RCC patients, according to categorizing patients in to two groups of high and low expressions.

tissues. The relation of PGGHG and ODF3B expression with demographic and clinicopathological features was assessed by Mann–Whitney and Kruskal-Wallis tests. In the next step, fold changes were divided into 2 groups of high and low expressions conforming to median for each gene, and the comparison among these groups were analyzed by chi-square test and independent t test. After surgery, we followed up patients until all-cause death used and censured alive one. The log rank test is a statistical hypothesis test that may be used to compare two high and low gene expression survival curves.

Results

TCGA data analysis

Using TCGA data we extracted 75 top upregulated genes in KIRC shown as heatmap in Figure 1A **(**extracted from UALCAN webserver (http://ualcan.path.uab.edu.), a heatmap containing some of these genes with similar patterns have been reported by Ping Wu et al. [9]. Then among theme, we selected only two uncharacterized genes with worse prognosis with reduced survival in KIRC (Figure 1A-C). Moreover, we investigated their expression in other two renal cancer types KIRP and KICH, which both genes showed lower-expression in KICH but over-expression in KIRP similar to the KIRC (Figure 1D and 1E). We also found that these two proteins can have indirect connections in the same protein network (Figure 2, using STRING), suggesting their possible roles in renal pathways and cancers. In addition to these data, its protein network revealed its interaction with several important proteins involved in biological pathways and cancers (including renal cancers), for instance, COL10A1 [10] (Figure 2). Based on these primary data we conducted our experimental study to identify the expression of these two genes in our patients with renal cancers.

Downregulation of PGGHG and ODF3B gene expression in RCC

Using qRT-PCR, the expression levels of mRNAs were assessed in 40 tumor samples and their tumor's adjacent normal tissues. As shown in the figure 3A, the expression level of *ODF3B* was significantly lower in tumors tissues (median=0.625) in comparison to the tumor's adjacent normal tissues (median=0.977) (P value=0.042). Also, the expression of *PGGHG* had significantly lower in tumor tissues (median=0.378) compared to their adjacent normal tissues (median=1.120) (Pvalue=0.034, Figure 3B).

Association between *PGGHG* and *ODF3B* gene expression and clinicopathological and demographic features of RCC

Next, we investigated the relationship between *PGGHG* and *ODF3B* expression levels and the clinicopathologic status of patients with renal cell carcinoma. Our results demonstrated that *ODF3B* had lower expression in RCC patients who had tumor size>4cm (P value=0.060, Figure 3C). When we divided fold changes into two high and low expressions groups, chi-square test proved the significant relation between tumor size and *ODF3B* expression (P value= 0.011, Table 2). Comparison of *PGGHG* expression level and tumor size did not show a significant difference (P value=0.744).

Since ccRCC is the most common of RCC and oncocytoma is the least common type in our study community (Table 1), our analysis showed that *PGGHG* expression level was higher in oncocytoma type in comparison to other type of RCC (P value=0.017, Figure 3D). Similarly, the relationship between the *ODF3B* expression level and the tumor type showed significant. The expression level of ODF3B was higher in oncocytoma type (P value=0.004, Figure 3E).

Functional enrichment analysis

Using Enrichr, we found down-regulation of ODF3B upon RUNX1 Knock-out mouse, PPARG deficiency mouse, SETDB1 Knock-down in THP1 human cells, IRF9 Knock-down in human cells, NANOG over-expressed mouse, and CREM Knock-out mouse (Supplementary Table 2). These data can suggest the possible upstream transcription factors of ODF3B which regulate its expression in biological pathways. Among GO ontologies using Enrichr, ODF3B was found to be involved in cytoskeleton (GO: 0005856, p-value: 0.03000) in

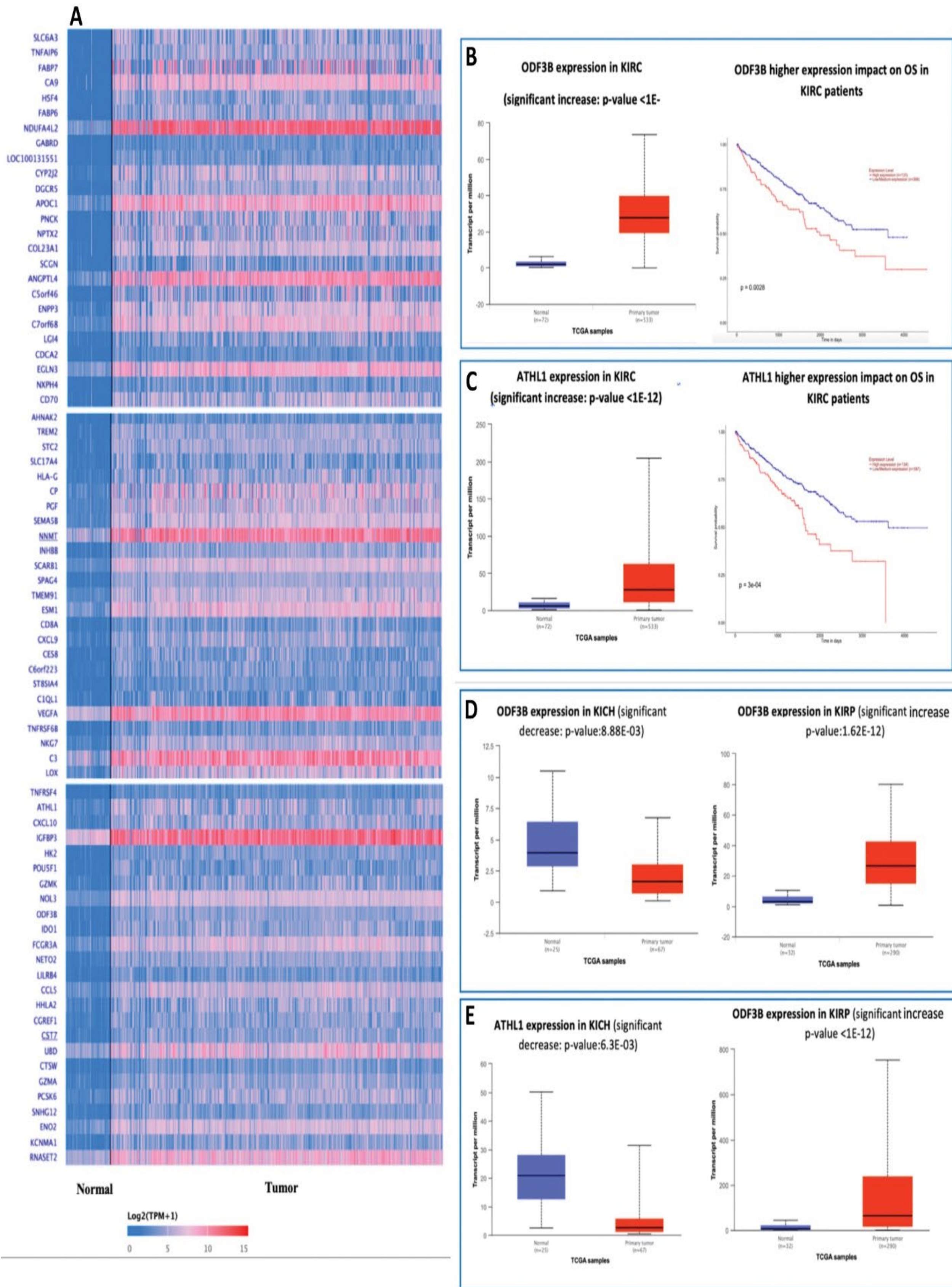

Figure 1: A. Seventy-five top upregulated genes in TCGA-KIRC from UALCAN webserver. **B.** Expression of *ODF3B* in KIRC and effect of its altered expression on OS in TCGA-KIRC. **C.** Expression of *PGGHG* in KIRC and effect of its altered expression on OS in TCGA-KIRC. **D.** Expression of *ODF3B* in KICH and KIRP. **E.** Expression of *PGGHG* in KICH and KIRP.

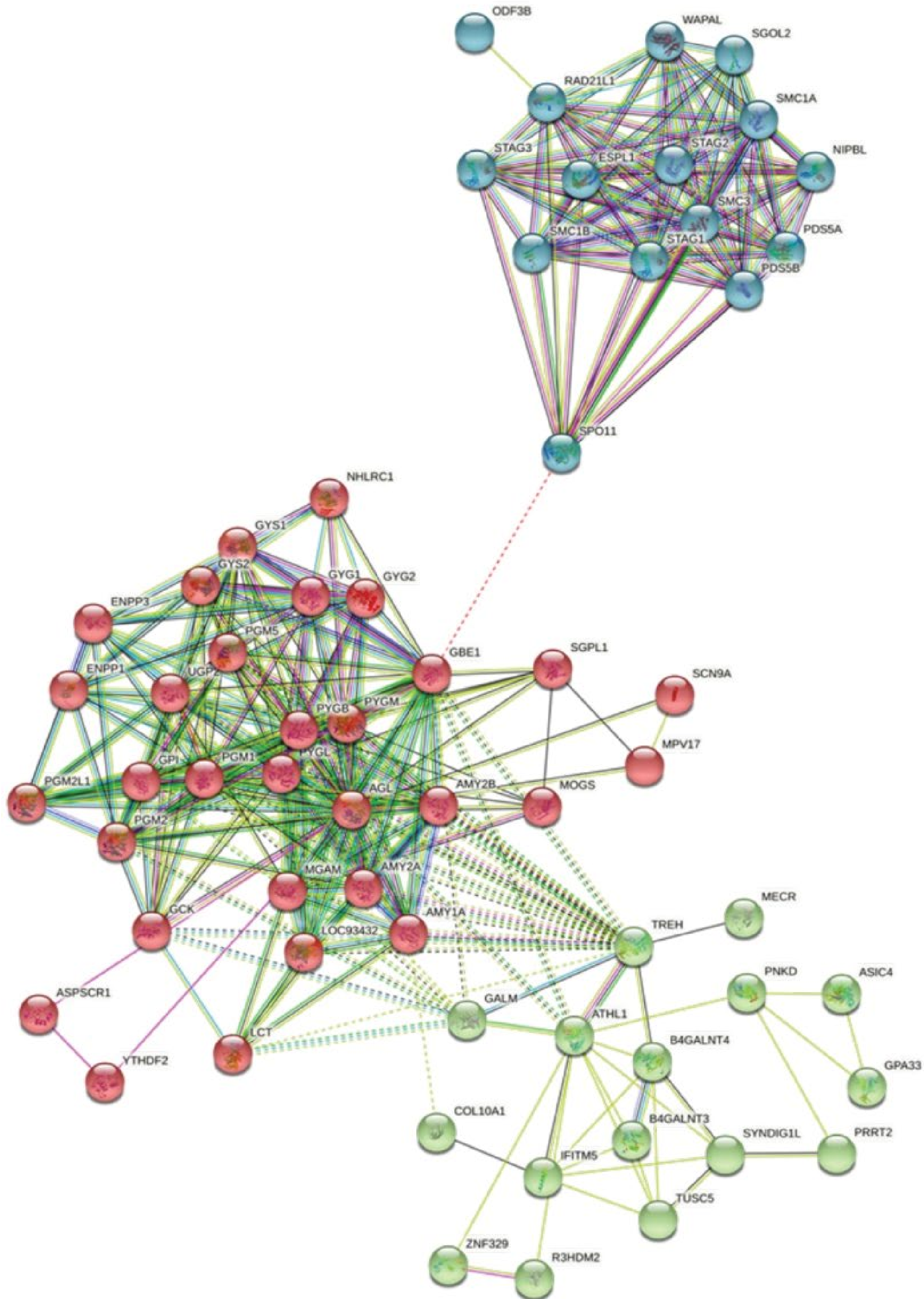

Figure 2. Protein network of PGGHG and ODF3B. It shows connection between protein networks of PGGHG and ODF3B, representing their possible roles in the same pathways and cancer pathogenesis.

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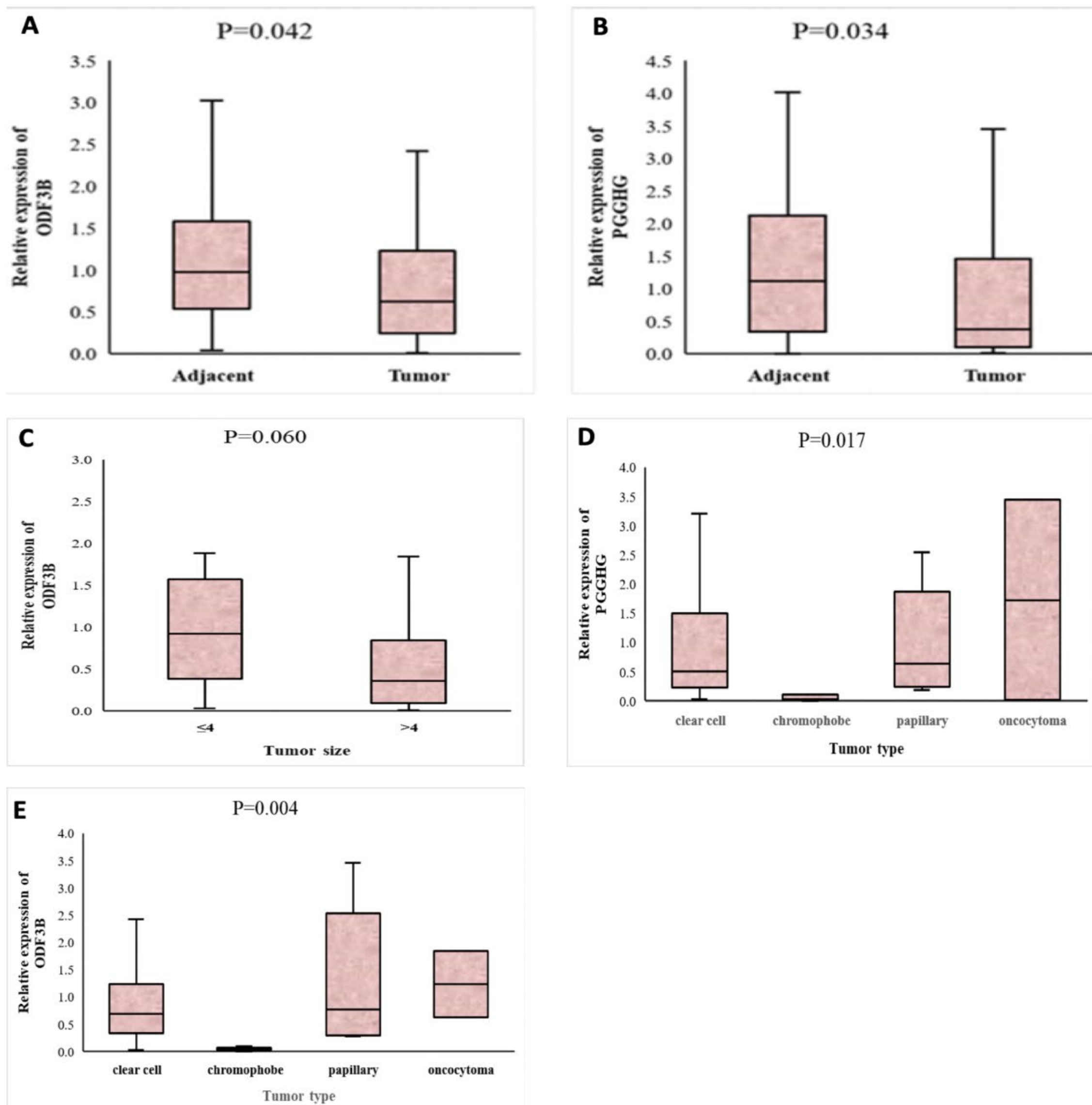

Figure 3: A and B. The boxplot of comparison of *PGGHG* and *ODF3B* expression between tumor samples and their paired adjacent normal tissues, respectively. **C.** The association between the expression of *ODF3B* and tumor size **D.** *PGGHG* expression levels in the different subgroups of tumor types in RCC. **E.** *ODF3B* expression levels in the different subgroups of tumor types in RCC.

terms of cellular component (CC).

In relation to the PGGHG, Enrichr revealed its down-regulation upon ZNF503 shRNA in H1 human cells, NFYC Knock-out in mouse, BCL6 Knock-down in human cells, POU2AF1 over-expression in mouse, EPAS1 Knock-down in HUVEC human cells, NFYA Knock-out in mouse, FOXP3 activation in human cells, PPARG over-expression in mouse, and GATA4 over-expression in A549 human cells (Supplementary Table 3). The interesting result was that while PPARG over-expression in mouse resulted in PGGHG down-regulation, PPARG deficiency mouse showed ODF3B down-regulation. These data may indicate PPARG as the same upstream transcription factor affecting ODF3B and PGGHG. Among GO using Enrichr, PGGHG showed involvement in hydrolase activity, hydrolyzing O-glycosyl compounds (GO: 0004553, p-value: 0.001850, in terms of molecular function (MF).

As shown in Figure 2, protein networks of PGGHG and ODF3B are connected and correlated. Therefore, we investigated the GO terms for all proteins involved in these networks to shed light on the identification of possible pathways of PGGHG and ODF3B.

Enrichr revealed significant KEGG, BP, MF, and CC for proteins involved in these networks given in Figure 4. However, the highest significant terms were as follow: **KEGG:** Starch and sucrose metabolism (p-value: 3.058e-43); **BP:** glucan biosynthetic process (GO:0009250, p-value: 5.259e-24), glycogen biosynthetic process (GO:0005978, p-value: 5.259e-24), and glycogen metabolic process (GO:0005977, p-value: 8.723e-27); **MF:** UDP-glucosyltransferase activity

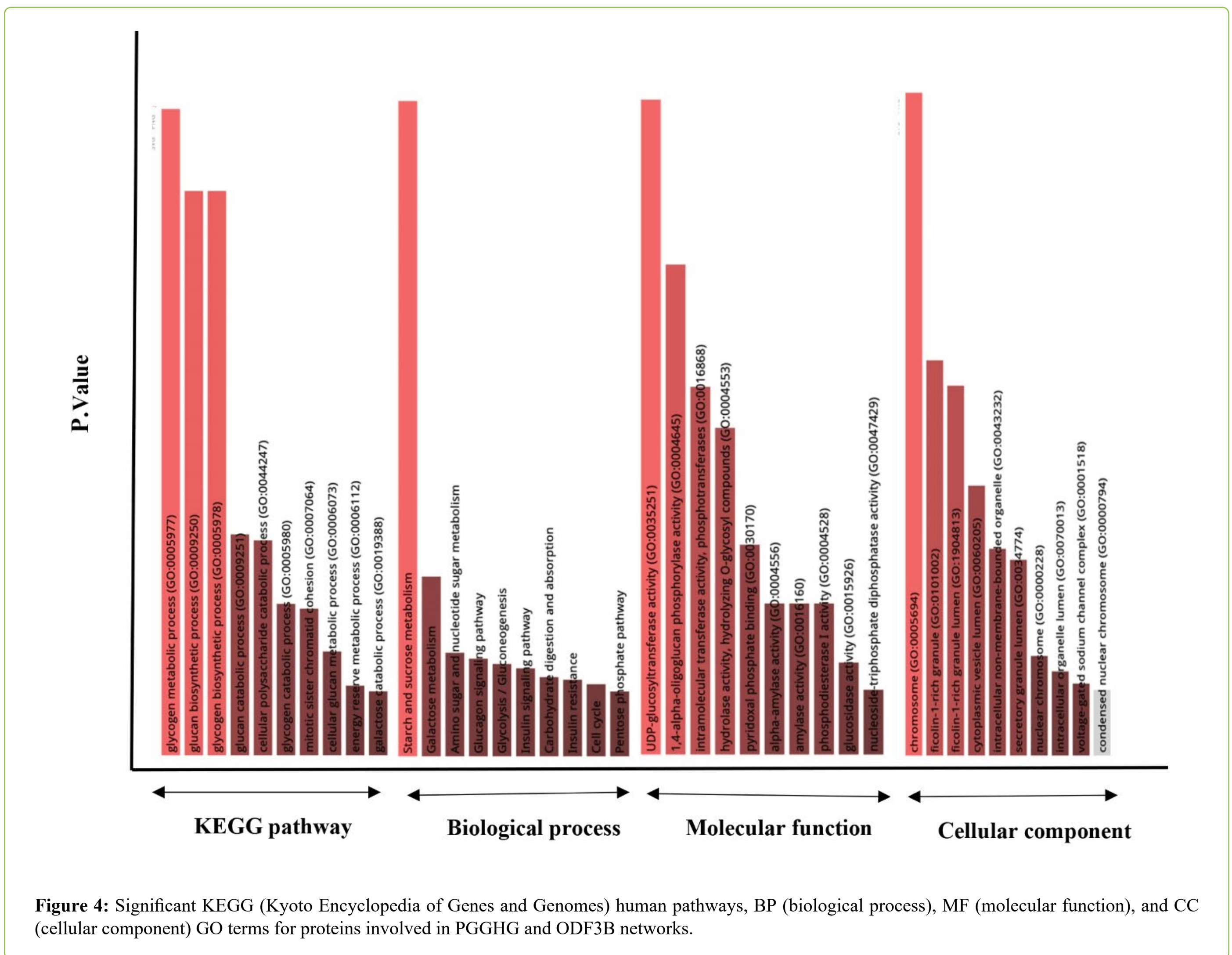

Figure 4: Significant KEGG (Kyoto Encyclopedia of Genes and Genomes) human pathways, BP (biological process), MF (molecular function), and CC (cellular component) GO terms for proteins involved in PGGHG and ODF3B networks.

(GO:0035251, p-value: 1.319e-8) and 1,4-alpha-oligoglucan phosphorylase activity (GO:0004645, p-value: 2.305e-7); **CC:** chromosome (GO:0005694, p-value: 1.921e-8). All information and proteins involved in these terms are provided in Supplementary file 1. These data may propose the possible roles of *PGGHG* and ODF3B, directly or indirectly, in these GO terms and KEGG pathways.

Overall survival

To evaluate survival analysis, we used the Kaplan–Meier method based on observed survival times. However, we were not able to predict the prognosis of renal cell carcinoma patients based on PGGHG and ODF3B gene expression using this data (Supplementary figure 1). The small proportion of participants evaluated, low duration of follow up and undetected exact cause of death could be some of the reasons.

Discussion

Renal cell carcinoma (RCC) is the most common form of kidney cancer and accounts for approximately 3.7% of the total cancer deaths [11]. Identification of biomarkers helps in improving the prognosis and early detection of RCC. Despite astonishing molecular advances and their significant impact on the detection of functional mRNAs in malignancies, numerous questions remain regarding molecular interactions and their function and need further attention.

In this study, we compared the *PGGHG* and *ODF3B* expression levels in tumor and their adjacent normal tissues in RCC patients and their association with demographical and clinicopathologic factors.

Our study with the use of QPCR as gold standard for relative expression analysis revealed the downregulated level of *PGGHG* and *ODF3B* in the tumor tissues compared to their adjacent normal tissues which were in contract to TCGA-KIRC. The reverse data for both genes in our experiments can strengthen the involvement of both proteinss in the same network. There are some reasons which might show these reverse results as follow: 1- The TCGA data is the raw data of RNA sequencing which usually are validated by gold standard approaches such as QPCR. Since in some genes the coverage is not optimal and may affect the correct overall gene expression. 2- Another factor which might affect the results is the population diversity since the TCGA data only has 8 KIRC samples from Asian region and we don't know how many samples are from Iranian population. 3- Other environmental factors and life styles in different area might change the expression of these genes. However, since our study showed lower expression

of these genes in all of our patients which was in contrast to TCGA data, more researches from different population with higher number of patients are needed to find whether different population, statuses, and other factors are involved in this reverse result, helping determination of the precise mechanism of their involvement in RCC pathogenesis.

Our results indicate that the expression level of *ODF3B* is significantly lower in tumor tissues than their normal adjacent ones. There are few investigations about the role of the studied genes in the development and progression of cancers. In the case of the *ODF3B* gene, an experimental study related to cancer has not been reported. Jihye Ryu et al. examine promotor activity of *ODF3B* in multiple sclerosis (MS) on large scale by genome-wide association studies (GWAS) signals. In this study, an association of promotor variants with the expression of this gene was reported [12]. In another study, Honglin Zhu et al. showed the *ODF3B* as potential methylation-regulated differentially expressed gene [13]. This gene delineates the abnormal activation of immune regulation in the pathogenesis of Systemic sclerosis (SSc).

Our study also showed significant lower expression of *PGGHG* in RCC tissues in comparison to their adjacent normal specimens. In the past decades, the role of aerobic glycolysis in cancer cells has been discussed, however, data supporting for glycogen biology in RCC are lacking [14]. In line with our results, a study demonstrated that reduced AGL, a glycogen debranching enzyme, increased tumor growth in patients with bladder cancer by RNA interference screen [15]. In another study, AGL loss led to the progression of bladder cancer. Details of this metabolomics pathway showed increased glucose metabolism with the help of serine hydroxymethyltransferase in cells [16].

Our data from Enrichr revealed significant KEGG, MF, BP, and CC for proteins involved in ODF3B and PGGHG networks, suggesting the possible roles of these two proteins, directly or indirectly, in these GO terms and KEGG pathways. Moreover, using Enrichr, we found the down-regulation of *ODF3B* and *PGGHG* upon perturbations of some transcription factors, mainly PPARG which affected both genes. PPARG, Peroxisome Proliferator Activated Receptor Gamma, is involved in adipocyte differentiation considered a "master regulator" of adipogenesis. Moreover, it represses inflammatory response genes in mouse macrophages [17,18]. We also identified the positive relationship of tumor size with the *ODF3B* expression level (Table 2). According to a study by Zhi et al., an increase in tumor size has been reported in the progression and high risk of lymph node metastases (LNM) in ccRCC [19].

Conclusion

In summary, we found lower expression of *ODF3B* and *PGGHG* in renal cancers and proposed their possible biological pathways and upstream transcription factors. Our results propose investigation of functional studies for *ODF3B* and *PGGHG* genes to identify their exact roles in biological pathways and cancers. While our study with the use of QPCR showed the lower-expression of *PGGHG* and *ODF3B* in our patients, they were in contract to TCGA-KIRC and some above-mentioned reasons might answer this reverse result. However, our study showed lower expression of these genes in all of our patients and further studies from different population with higher number of patients are needed to investigate the expression of these genes in renal cancers to uncover the exact role of them in these cancers.

Authors' Contributions

Conceptualization: [Elham Mohammadisoleimani]; Methodology: [Elham Mohammadisoleimani, Zahra Firoozi, and Hassan Dastsooz]; Formal analysis and investigation: [Hassan Dastsooz , Mohammad Mehdi Naghizadeh, and Elham Mohammadisoleimani]; Writing - original draft preparation: [Elham Mohammadisoleimani, Hamed Haghi-Aminjan, Hassan Dastsooz, and Zahra Firoozi]; Writing - review and editing: [Hassan Dastsooz, Abdolreza Daraei, and Yaser Mansoori]; Funding acquisition: [Yaser Mansoori], Resources: [Shahryar Zeighami, Ali Ariafar, Hosein Mansoori]; Supervision: [Yaser Mansoori]. All authors read and approved the manuscript before submission.

Ethical Statements

The local ethical committee at Fasa University of Medical Sciences (ethical code: IR.FUMS.REC.1398.147) approved this study.

Conflict of interest

None. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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