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Increased PYCR1 mRNA predicts poor prognosis in kidney adenocarcinoma

A study based on TCGA database

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Abstract

The pyrroline-5-carboxylate reductase 1 (PYCR1) plays important roles in cancers, but its contribution to adenocarcinoma of the kidney (AK) and the potential mechanism remain to be clarified. In this study, we aimed to demonstrate the relationship between PYCR1 mRNA and AK based on The Cancer Genome Atlas database.

PYCR1 mRNA in AK and normal tissues was compared using Wilcoxon rank sum test. The relationship between PYCR1 mRNA and clinicopathological characters was evaluated using logistic regression. The association between PYCR1 mRNA and survival rate was evaluated using Kaplan-Meier test and Cox regression of univariate and multivariate analysis. Additionally, Gene Set Enrichment Analysis was conducted to annotate the biological function of PYCR1 mRNA.

Increased PYCR1 mRNA was found in AK tissues. Increased PYCR1 mRNA was related to high histologic grade, clinical stage, and lymph node and distant metastasis. Kaplan-Meier survival analysis and univariate analysis showed that AK patients with increased PYCR1 mRNA had worse prognosis than those without. PYCR1 mRNA remained independently associated with overall survival (HR: 1.34; 95% CI: 1.07–1.66; $P = .009$) in multivariate analysis. The Gene Set Enrichment Analysis suggested that ribosome, proteasome, inhibition of p53 signaling pathway, extracellular matrix receptor interaction, and homologous recombination were differentially enriched in increased PYCR1 mRNA phenotype.

Increased PYCR1 mRNA is a potential marker in patients with AK. More importantly, p53 pathway, ribosome, proteasome, extracellular matrix receptor interaction, and homologous are differentially enriched in AK patients with increased PYCR1 mRNA.

Abbreviations: AK = adenocarcinoma of the kidney, GSEA = Gene Set Enrichment Analysis, PYCR1 = pyrroline-5-carboxylate reductase 1, TCGA = The Cancer Genome Atlas.

Keywords: adenocarcinoma, GSEA, kidney prognosis, PYCR1, TCGA

1. Introduction

Adenocarcinoma of the kidney (AK), also known as renal cell carcinoma, mostly originates from renal tubular epithelial cells. AK is one of the most common malignant tumors of urinary system, and is the ninth most common malignant tumor in Western countries with about 403,000 new cases and 175,000 deaths worldwide reported every year.[1] The incidence of AK has been steadily increasing by 2% to 4% each year and the mortality rate has also been increasing.[2] AK is insensitive to traditional radiotherapy and chemotherapy, which only improves a survival rate of less than 10% in 5 years after disease metastasis.[3] Currently, surgical resection is the most effective treatment for

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early-stage AK. Most patients have AK cancer of stage I and have the best prognosis, whereas AK patients of stage III and stage IV have worse prognosis.[4] Additionally, there are no effective biomarkers for prognosis and for direct treatment (adjuvant radiation and/or chemotherapy) of AK. Therefore, novel approaches for diagnosis, treatment, and prognosis of AK are needed.

Proline is a unique and non-essential amino acid in humans, which has been recognized as a structural disruptor and indicator of various pathological stresses during tumorigenesis.[5,6] The metabolism and synthesis of proline are involved in tricarboxylic acid cycle, urea cycle, and pentose phosphate pathway.[7,8] Proline also plays key roles in cellular signaling processes, cellular bioenergetics, and cancer cell metabolism.[9–11] Dehydrogenase/oxidase is the first enzyme of proline catabolism, and pyrrole-5-carboxylate reductase (PYCR) is the final key enzyme that catalyzes the synthesis of proline, including PYCR1, PYCR2, and PYCR like.[12] It has been demonstrated that PYCR1 may play an important role in tumorigenesis.[13–15] PYCR1 is overexpressed in breast cancer, prostate cancer, and lung cancer cells, whereas silencing PYCR1 suppresses tumor cell proliferation and survival.[13,15] Recent studies indicate broad effects of proline metabolism on cancer cell growth and survival, which suggests that proline metabolic enzymes can serve as potential targets for therapeutic intervention.[13,15–17] However, the correlation between PYCR1 and the prognosis of AK has not been reported.

In this study, we explored the potential relations between PYCR1 mRNA and AK using the data from The Cancer Genome Atlas (TCGA) database. The relationship of PYCR1 with prognosis of AK was evaluated. The PYCR1-related biological pathways that involved in AK pathogenesis were analyzed. Our findings demonstrate that the increased PYCR1 mRNA may be associated with poor survival of AK.

2. Material and methods

The study is systematic review, so ethical approval and patient consent are not needed.

2.1. Bioinformatics analysis

The gene expression data (941 cases, Workflow Type: HTSeq-FPKM) and corresponding clinical information were downloaded from TCGA database (https://portal.gdc.cancer.gov). Boxplots were used to visualize differential expressions between discrete variables.[13] The RNA-Seq data and clinic data of 539 patients with AK were used for further analysis.

2.2. Gene set enrichment analysis

A list of genes according to their correlation with PYCR1 mRNA was generated using Gene Set Enrichment Analysis (GSEA).[14] The mRNA level of PYCR1 was used as a phenotype label. The nominal *P* value and normalized enrichment score were used to sort the pathways enriched in each phenotype.

2.3. Statistical analysis

All statistical analyses were conducted using R package (v.3.6.1). The relationship between clinical pathologic features and PYCR1 mRNA was analyzed using the Wilcoxon signed-rank test and logistic regression. The relationship between clinicopathologic characteristics associated with overall survival of patients was analyzed using Cox regression of univariate analysis and the Kaplan-Meier methods. Multivariate Cox analysis was used to compare the effect of PYCR1 mRNA on survival as well as other clinical characteristics (stage, grade, histology, myometrial invasion, lymph node metastasis, and distant metastasis). The cutoff value of PYCR1 mRNA was determined by its median value. $P < .05$ was considered as statistically significant.

Table 1

Clinicopathological characteristics of patients with adenocarcinoma of the kidney.

Clinical characteristics		Total (941)	%
Age at diagnosis (yrs)		54 (17–90)	
Gender	Male	622	66.1
	Female	319	33.9
Status	With tumor	539	88.2
	Tumor free	72	11.8
Histologic grade	Well	14	2.5
	Moderate	230	43.6
	Poor	282	53.9
Stage	I	265	50.4
	II	54	10.3
	III	124	23.6
	IV	83	15.7
Histology	Adenocarcinoma	539	100.0
Vital status	Alive	707	75.1
	Dead	234	24.9
Lymph nodes	Negative	338	86.9
	Positive	51	13.1
Distant metastasis	Negative	555	86.0
	Positive	90	14.0

3. Results

3.1. Clinicopathologic characteristics of AK patients from TCGA

The clinical data and gene expression data in 941 patients with primary AK tumors were downloaded from TCGA in January 2020 and shown in Table 1. Their median age was 54 (range 17–90) years old. For histologic grade, 14 (2.5%) cases were with well differentiated AK tumors, 230 (43.6%) were with moderately differentiated, and 282 (53.9%) were with poorly differentiated. For tumor status, 72 patients were of tumor-free (11.9%) and 539 were with tumors (88.1%). For tumor clinical TNM stage, 265 patients were with stage I tumor (50.4%), 54 were with stage II (10.3%), 124 were with stage III (23.6%), and 83 were with stage IV (15.7%). Additionally, 51 (13.1%) cases had lymph node metastases (pelvic and para-aortic), and 90 (14.0%) cases had distant metastases. The median follow-up time for subjects alive at last contact was 30.7 months (range 0–198 months).

3.2. Association between PYCR1 mRNA and clinicopathologic characteristics

A total of 941 AK samples from TCGA with PYCR1 mRNA expression were analyzed. As shown in Figure 1A and B, PYCR1 mRNA was increased in tumor samples, and correlated significantly with clinical TNM stage ($P < .001$) (Fig. 1C). The

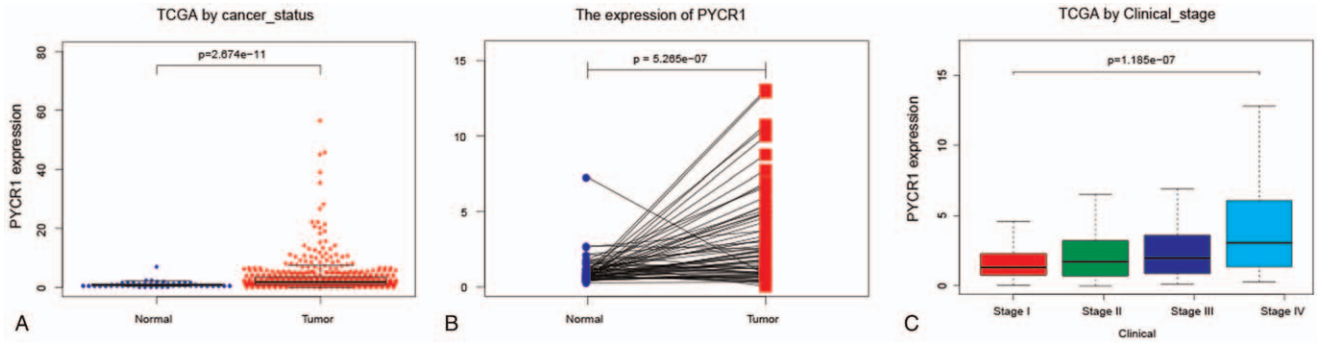

Figure 1. Association of PYCR1 mRNA expression and clinicopathologic characteristics. (A) PYCR1 mRNA was prominently overexpressed in AK ($P < .001$) (normal, n = 72; tumor, n = 539); (B) PYCR1 mRNA was prominently overexpressed in AK (n = 72) ($P < .001$) compared with 72 pairs normal adjacent tissues using Wilcoxon singed rank test; (C) Association of PYCR1 expression and clinical stage. PYCR1 mRNA was prominently overexpressed in stage IV (n = 526). AK = adenocarcinoma of the kidney, PYCR1 = pyrroline-5-carboxylate reductase 1.

cutoff value of PYCR1 mRNA expression, which was determined based on the median value, was 2.2. Univariate analysis using logistic regression revealed that, as a categorical dependent variable, PYCR1 mRNA was associated with poor prognostic clinicopathologic characteristics (Table 2). In detail, increased PYCR1 mRNA in AK was significantly associated with high histologic grade (OR = 2.8 for well, moderate vs poor), clinical stage (OR = 4.0 for IV vs I), and distant metastasis (OR = 3.0 for positive vs negative) ($P < .05$). These results suggest that AK with increased PYCR1 mRNA is prone to progress to a more advanced stage than those without.

3.3. Survival analysis

Based on the cutoff value of *PYCR1*, the patients were grouped into those with increased PYCR1 expression (n = 539) and those without (n = 72). Kaplan-Meier survival analysis showed that AK patients with increased PYCR1 mRNA had a worse prognosis than those without (Fig. 2A, $P < .001$). The univariate analysis revealed that increased PYCR1 mRNA correlated with a poor overall survival significantly (HR: 1.05, 95% CI: 1.03–1.07; $P < .001$) (Table 3). Other clinicopathologic variables associated with poor survival included advanced stage, positive lymph nodes, distant metastasis, and deep myometrial invasion (Table 3). Multivariate analysis showed that PYCR1 mRNA remained significant association with overall survival independently (HR: 1.36, 95%CI: 1.08–1.66; $P = .009$) (Fig. 2B).

3.4. GSEA identifies PYCR1-related signaling pathways

To identify signaling pathways that are differentially activated in AK, we conducted GSEA analysis between data sets with decreased and increased PYCR1 mRNA. The enrichment plots from GSEA were shown in Figure 3, in which each curve represents a pathway. GSEA revealed significant differences in the enrichment of MSigDB Collection (c2.cp.kegg.v6.2.symbols.gmt) between the 2 datasets (FDR $q < 0.25$, NOM P value $< .05$). We selected the most significantly enriched signaling pathways based on their normalized enrichment score and showed them in Table 4 and Figure 3. Ribosome, proteasome, p53 pathway, ECM receptor interaction, and homologous recombination were differentially enriched in elevated PYCR1 mRNA phenotype (Table 4 and Fig. 3).

Table 2

Association of PYCR1 expression with clinical pathological characteristics.

Clinical characteristics	Total (n)	OR (95% CI)	*P* value
Grade (well or moderate vs poor)	526	2.8 (1.45–4.96)	.000
Stage (IV vs I)	348	4.0 (2.36–7.08)	.000
Status (tumor free vs with tumor)	601	2.3 (1.28–3.87)	.000
Distant metastasis (positive vs negative)	645	3.0 (1.03–5.64)	.000
Lymph node metastasis (positive vs negative)	141	3.2 (1.08–11.74)	.049

PYCR1 = pyrroline-5-carboxylate reductase 1.

4. Discussion

As a member of PYCR, PYCR1 is highlighted in the biosynthesis of proline in various tumors. For instance, PYCR1 cooperates with isocitrate dehydrogenase 1 to promote cancer cell survival in glioma and esophageal squamous cell cancer.[18,19] PYCR1 is screened out in 19 cancers and proposed as a novel enzyme.[20] PYCR1 is overexpressed in several cancer tissues, suggesting that it may be closely related to the development and progression of cancer.[13,14,21] However, the expression and related functions of PYCR1 in AK are still unclear.

In this study, we collected high throughput RNA sequencing data of AK from TCGA database and demonstrated that PYCR1 mRNA was significantly up-regulated in AK tissues compared with normal kidney tissue or adjacent normal tissues of kidney cancer. Moreover, increased PYCR1 mRNA in AK was positively correlated with high clinical stage and poor prognosis. Univariate and multivariate Cox analyses indicated that the PYCR1 mRNA may be a useful biomarker for AK prognosis. Furthermore, we investigated the function of PYCR1 in kidney cancer tissues using GSEA, and showed that the p53 pathway, ribosome, proteasome, the ECM receptor interaction, and homologous recombination were found differentially and significantly enriched in increased PYCR1 mRNA phenotype. These pathways, especially the p53 pathway, are reported to contribute to cancer cell proliferation, invasion, and metastasis.[22–24] This implies the potential role of PYCR1 as prognostic target in AK. A recent study reported that a fraction of kindlin-2 localized to mitochondria and interacted with PYCR1.[25] ECM stiffening promoted kindlin-2 translocation into mitochondria, resulted in elevation of PYCR1 expression and thus increased proline synthesis and cell proliferation. Depletion of kindlin-2 reduced PYCR1 level, increased reactive oxygen species

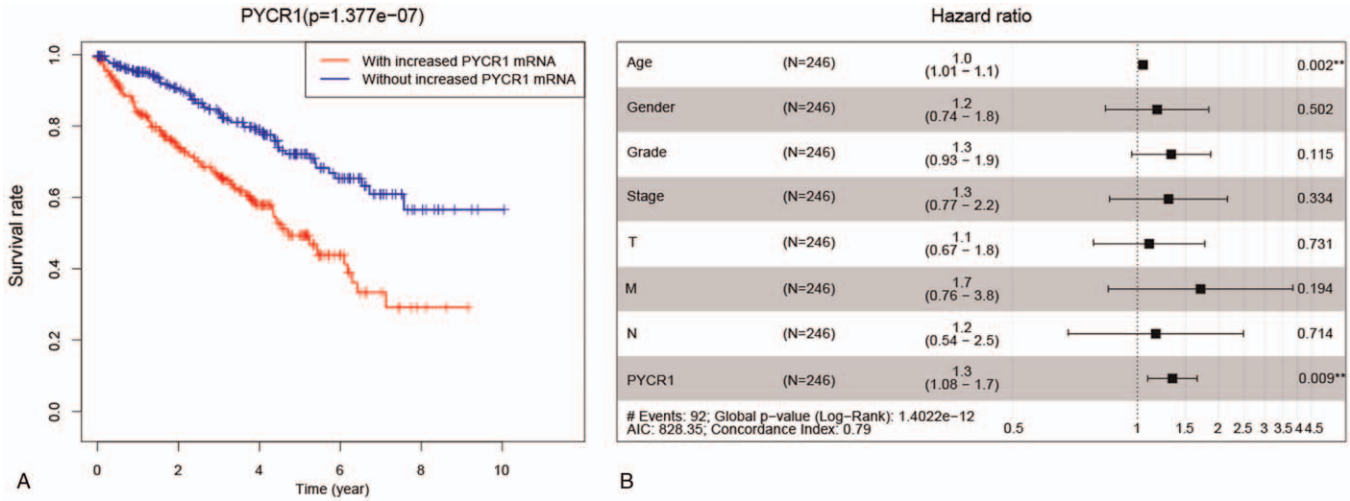

Figure 2. Survival analysis. (A) Association between PYCR1 mRNA and survival rate (n = 539). (B) Hazard ratio with multivariate survival model (n = 246). PYCR1 = pyrroline-5-carboxylate reductase 1.

Table 3

Association between overall survival and clinicopathologic characteristics of patients.

Clinical characteristics	HR (95% CI)	*P* value
a		
Age (continuous)	1.02 (1.00–1.04)	.012
PYCR1 expression (high vs low)	1.05 (1.03–1.07)	.000
Grade (well or moderate vs poor)	2.24 (1.68–2.99)	.000
Stage (IV vs I)	1.86 (1.54–2.25)	.000
Distant metastasis (positive vs negative)	1.94 (1.53–2.46)	.000
Lymph nodes (positive vs negative)	2.93 (1.51–5.67)	.000
b		
PYCR1 expression (high vs low)	1.36 (1.08–1.66)	.009
Myometrial invasion (≥50% vs <50%)	1.71 (0.76–3.84)	.194
Age (continuous)	1.03 (1.01–1.05)	.002

a: Categorical dependent variable, greater or less than the median expression level.

b: Multivariate survival model after variable selection.

PYCR1 = pyrroline-5-carboxylate reductase 1.

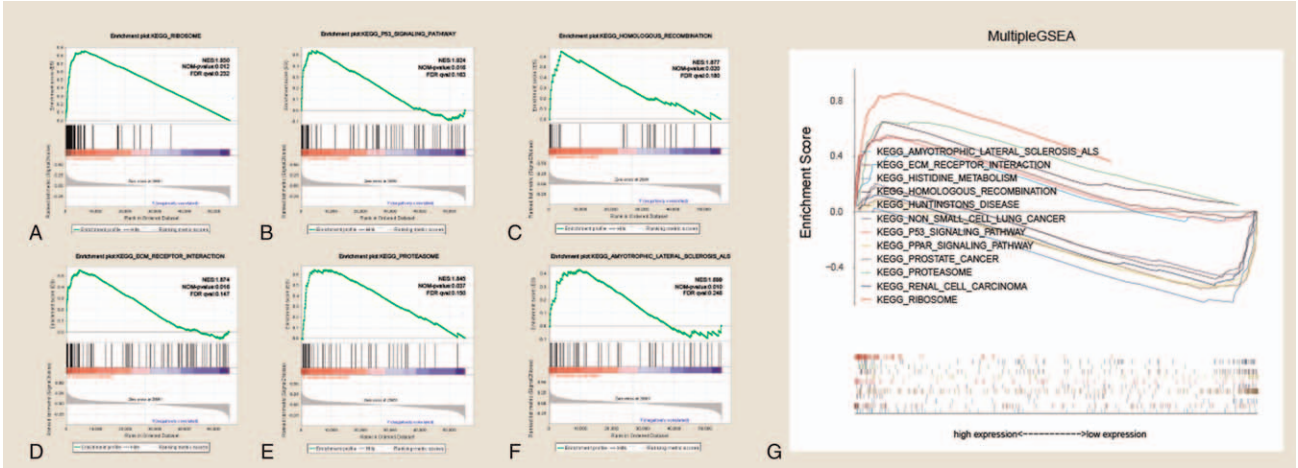

Figure 3. Enrichment plots from Gene Set Enrichment Analysis (GSEA). Ribosome (A), p53 signaling pathway (B), homologous recombination (C), extracellular matrix receptor interaction (D), proteasome (E), and ALS (F) were differentially enriched in PYCR1-related AK, adenocarcinoma of the kidney. (G) Enrichment plots from gene set enrichment analysis (GSEA). Each curve represents a pathway. ES = enrichment score, NES = normalized enrichment score, NOM p-val = normalized *P* value, PYCR1 = pyrroline-5-carboxylate reductase 1.

Table 4

Gene sets enriched in highly expressed PYCR1 phenotype.

MSigDB collection	Gene set name	NES	NOM *P* value	FDR *q*-value
c2.cp.kegg.v6.2.symbols.gmt	RIBOSOME	1.930	.012	0.232
	P53_SIGNALING_PATHWAY	1.924	.016	0.163
	HOMOLOGOUS_RECOMBINATION	1.877	.020	0.180
	Extracellular matrix _RECEPTOR_INTERACTION	1.874	.016	0.147
	PROTEASOME	1.845	.037	0.150
	AMYOTROPHIC_LATERAL_SCLEROSIS_ALS	1.699	.010	0.246

Gene sets with NOM p-val $< .05$ and FDR q-val < 0.25 are considered as significant.
FDR = false discovery rate, NES = normalized enrichment score, NOM = nominal, PYCR1 = pyrroline-5-carboxylate reductase 1.

production and apoptosis, and abolished ECM stiffening-induced proline synthesis and cell proliferation.[25] A mechanoresponsive kindlin-2-PYCR1 complex that linked mechano-environment to proline metabolism and signaling was also revealed, suggesting its potential to inhibit tumor growth. Moreover, PYCR1 promotes ECM adhesion, actin cytoskeletal contraction, cell survival, proliferation, metabolic reprograming, and collagen matrix deposition in both lung adenocarcinoma cells and associated fibroblasts, which collectively contribute to the progression of lung adenocarcinoma.[25]

Our results also indicate that PYCR1 mRNA alterations may be associated with ribosome, proteasome and p53 signaling pathway in AK. The ribosome is the place for protein synthesis and known as the "protein factory of cells".[26] The ubiquitin-proteasome system has a central role in regulating protein activities as well as cell cycle, gene expression, oxidative stress response, cell survival, cell proliferation, and apoptosis.[27] The p53, previously described as a tumor suppressor, is now considered to be a key component of the mitochondrial apoptosis pathway under cell stress.[28] In response to various stimuli such as hypoxia, DNA damage, and reactive oxygen species, the p53 pathway induces cell death through activation of target genes and transcriptional-independent signal mechanism.[28] It has been reported that silencing of PYCR1 results in activation of p53 pathway and cell cycle arrest in hTERT-immortalized human foreskin fibroblasts.[12] To our knowledge, our work is the first report on the association of PYCR1 mRNA with the p53 pathway, ribosome, and proteasome. However, the prediction of protein expression using RNA-Seq data is far from perfect.[29] Because of limitations in our study design, the correlation between PYCR1 mRNA and PYCR1 protein expression could not be clearly assessed in this report. Further studies on direct mechanisms of PYCR1 in AK are needed.

In conclusion, PYCR1 may be a potential prognostic molecular marker of poor survival in AK. Moreover, the p53 signaling pathway, ribosome, and proteasome may be related to PYCR1 mRNA alteration in AK.

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Author contributions

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