BMC Urology

RESEARCH

Open Access

Retinoid X receptor γ predicts the prognosis and is associated with immune infiltration in kidney renal clear cell carcinoma: a qRT-PCR, TCGA and in silico research

Jianda Dong[1†], Lailai Fan[2†], Qiaolin Wu[3] and Zhouci Zheng[1*]

Abstract

Background Kidney clear cell carcinoma (KIRC) stands as one of the most prevalent primary malignant tumors, showcasing significant heterogeneity within the urological system. However, the precise molecular mechanisms underpinning tumorigenesis in KIRC remain elusive. While Retinoid X receptor γ (RXRG) has been implicated in various diseases and human cancers, its specific role in KIRC remains undetermined. This research aimed to investigate the involvement of RXRG in KIRC pathogenesis.

Methods Quantitative real-time polymerase chain reaction was performed to evaluate the expression levels of RXRG in KIRC. Utilizing RNA-seq data and corresponding clinicopathological information from The Cancer Genome Atlas (TCGA) database, we embarked on an analysis to ascertain the prognostic significance of RXRG in KIRC. Furthermore, bioinformatics analyses were employed to delineate the preliminary molecular mechanisms through which RXRG operates in KIRC tumorigenesis.

Results Our findings revealed a significant downregulation of RXRG in KIRC tumor tissues compared to normal kidney tissues, as evidenced in local and TCGA cohorts. Diminished RXRG expression correlated with adverse clinicopathological characteristics, including larger tumor size, higher clinical stage, and advanced histologic grade. Cox regression analyses unveiled that reduced RXRG expression was associated with poorer overall survival (OS) and disease-free survival (DFS) rates in KIRC patients. Bioinformatics analyses indicated that the RXRG-related differentially expressed genes (DEGs) were involved in tumorigenesis and metabolism by regulating a series of signaling pathways. Using ssGSEA, we found that RXRG expression was significantly associated with NK cells and macrophages.

Conclusion Our study provides new insights and evidence that RXRG is involved in the tumorigenesis of KIRC and may be a suitable target for immunotherapy in KIRC.

Keywords Kidney renal clear cell carcinoma, RXRG, Prognosis, Immune infiltration

†Jianda Dong and Lailai Fan contributed equally to this work.

*Correspondence:
Zhouci Zheng
424505514@qq.com
[1]Department of Neck Surgery, The Second Affiliated Hospital, Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
[2]Department of Urinary Surgery, The Second Affiliated Hospital and Yuying, Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
[3]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Renal cell carcinoma (RCC) stands as the most prevalent carcinoma affecting the urological system globally, comprising 2–3% of adult malignant tumors [1]. In 2022, approximately 77,410 cases of renal cell cancer were diagnosed in China, and approximately 46,345 patients succumbed to the disease [2]. Approximately 81,800 estimated new cases and 14,890 estimated deaths from this cancer occurred in American in 2024 [3]. Kidney renal clear cell carcinoma (KIRC) emerges as the predominant subtype of RCC, constituting over 80% of all RCC cases [4].

Although most patients are diagnosed at the early stages, about one-third of patients present with metastases at the time of initial diagnosis [5]. Despite substantial research and advancements in KIRC-targeted therapies [6], improving the overall survival (OS) and disease-free survival (DFS) of patients remains a paramount clinical task [7, 8]. Therefore, the quest for novel potential markers within KIRC may offer fresh insights into prognostic forecasting and personalized therapeutic interventions.

Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are members of the nuclear receptor superfamily. By acting via retinoids, they can regulate cell differentiation and proliferation [9, 10]. RXRA, RXRB, and RXRG are subtypes of RXRs, which can subdue cancer progression and disturb cellular proliferation [11, 12]. Abnormal expression of RXRG can lead to certain diseases [13–16]; however, the role of RXRG in KIRC prognosis remains ambiguous.

This study aims to evaluate the relationship between RXRG expression and clinicopathological factors in KIRC by utilizing a large-scale sample cohort. Furthermore, the prognostic significance of RXRG in KIRC patients will be scrutinized, alongside a preliminary exploration of the potential molecular mechanisms underlying RXRG's involvement in KIRC tumorigenesis.

Materials and methods

Clinical samples

A total of 14 tissues from clinical cases of KIRC tumors and matched noncancerous kidney tissues were procured during surgeries from February 2019 to June 2019 at the Second Affiliated Hospital of Wenzhou Medical University. All samples were promptly snap-frozen after resection and stored at − 80 °C for subsequent RNA isolation. Histological diagnosis confirmation was carried out by two senior pathologists utilizing a double-blind method. All participants provided informed consent for the scientific utilization of biological material before sample collection. This research protocol was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University.

Detection of RXRG expression by quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA extraction from the paired KIRC tumors and noncancerous kidney tissues was performed using TRIzol reagent (Life Technologies, Carlsbad, CA). The cDNA synthesis was carried out using the ReverTra Ace qPCR RT Kit (Toyobo, Osaka, Japan). Subsequently, qRT-PCR analysis of RXRG expression was conducted in triplicate utilizing the Thunderbird SYBR qPCR Mix (Toyobo, Osaka, Japan), with GAPDH expression serving as the internal control.

Dataset source

The clinical data and corresponding RNA-seq data of RXRG, including 541 KIRC tumors and 72 normal kidney tissues, were downloaded from the Cancer Genome Atlas (TCGA) database. The E-MTAB-1980 dataset [17] was obtained from the EMBL-EBI database (https://www.ebi.ac.uk/).

Prognostic analysis of RXRG in KIRC

Univariate Cox regression analysis was conducted to assess the association between RXRG expression and the prognosis of KIRC patients using the survival package. Kaplan–Meier (KM) survival curves were plotted to compare the prognosis of patients with different RXRG expression levels. Visualization was accomplished with the ggplot2 package and survminer package in R software version 3.6.4.

Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Protein-Protein Interaction (PPI) analyses

GO and KEGG analyses of RXRG in KIRC were performed with the clusterProfiler package, and a *P*-value of less than 0.05 was considered statistically significant. PPI analyses were performed in STRING [18] (version 12.0) to explore protein interactions and propose potential pathways through which RXRG may be involved in KIRC. Cytoscape version 3.9.1 was used for hub gene analysis. With|NES| > 1 and a *P*-value of less than 0.05 as the threshold for gene set enrichment analysis (GSEA), the pathways were considered significantly enriched when they met the sub-conditions.

Tumor immune infiltration analysis

The data of KIRC immune infiltration was downloaded from the TCGA database. The single-sample gene set enrichment analysis (ssGSEA) from the R package was used to evaluate the correlation between RXRG expression and immune cells.

Statistical analysis

Differences in expression between KIRC tumor tissues and noncancerous kidney tissues were assessed using the Mann-Whitney U test. The relationship between clinicopathological characteristics and RXRG expression was assessed using the chi-square test or Fisher's exact test. All *P*-values were two-sided, and a *P*-value of less than 0.05 was considered statistically significant. The statistical analysis was conducted using SPSS version 20.0 (Chicago, IL, USA).

Results

Clinicopathological factors of local patients with KIRC

This study involved 14 patients, including 8 men (57.1%) and 6 women (42.9%) (male-to-female ratio = 1.33). The patients were 34–74 years of age at diagnosis with a mean age of 56.1 years. Among them, three patients suffered from lymph node metastasis (LNM), and none had distant metastasis (DM) (Supplementary Table 1). No significant difference was observed between the local and TCGA cohorts due to the small case series of the former.

RXRG expression was downregulated in KIRC

The expression pattern of RXRG was examined in 14 pairs of KIRC tumors and matched normal kidney tissues. As shown in Fig. 1A, RXRG expression was significantly downregulated in the tumor samples compared with that in normal samples ($P < 0.01$). This result was consistent with the TCGA data, where RXRG expression was lower in KIRC samples than in normal kidney samples ($P < 0.01$, Fig. 1B).

Relationship between RXRG expression and clinicopathological features in KIRC

The relationship between RXRG expression and clinicopathological factors in KIRC was analyzed. The 541 patients with KIRC from the TCGA database were divided into low ($n = 270$) and high ($n = 271$) RXRG expression groups on the basis of the median value. The results revealed that low RXRG expression was significantly associated with larger tumor size ($P < 0.001$), high clinical stage ($P = 0.011$), and advanced histologic grade ($P = 0.003$) (Table 1). However, no significant difference was observed between RXRG expression and age, gender, race, pathologic N stage, or pathologic M stage ($P > 0.05$).

Low RXRG expression was associated with worse prognosis in KIRC

The prognostic role of RXRG in KIRC patients was investigated through Cox regression analyses. The results revealed that age (HR = 1.791, 95% CI = 1.319–2.432, $P < 0.001$), pathologic T stage (HR = 3.210, 95% CI = 2.373–4.342, $P < 0.001$), pathologic N stage (HR = 3.422, 95% CI = 1.817–6.446, $P < 0.001$), pathologic M stage (HR = 4.401, 95% CI = 3.226–6.002, $P < 0.001$), histologic grade (HR = 2.665, 95%

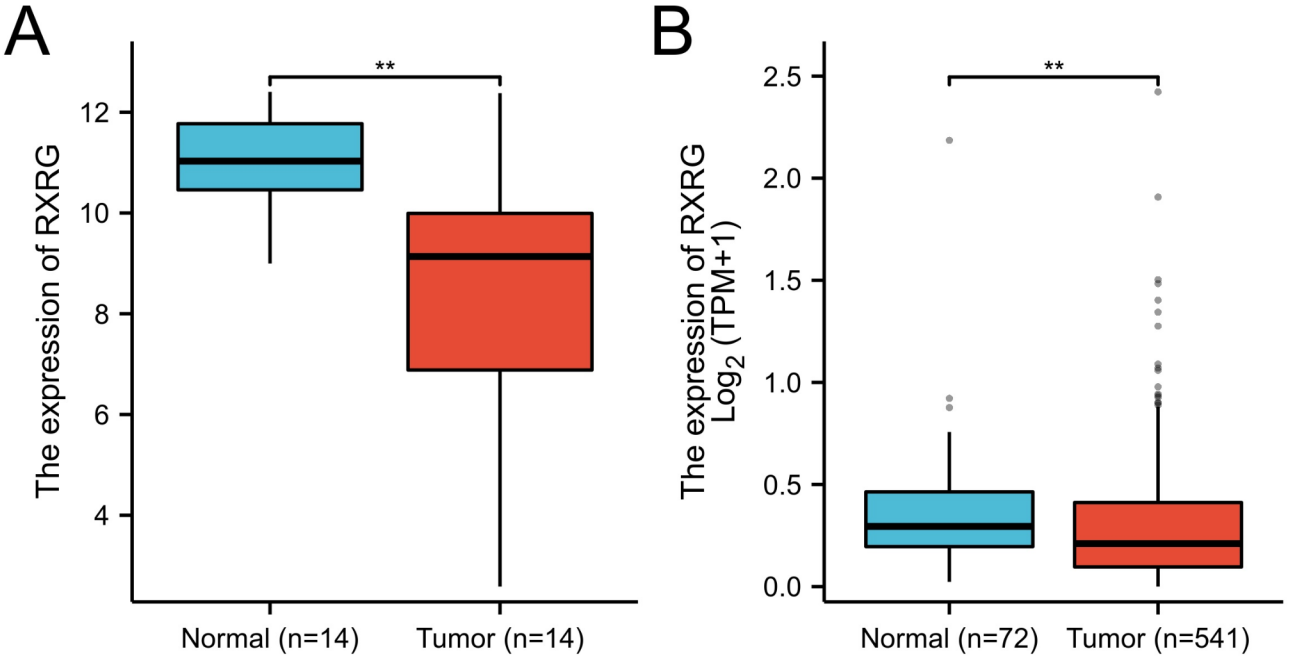

Fig. 1 RXRG expression was significantly downregulated in KIRC samples compared with normal kidney tissues in local and TCGA cohorts. Notes: (**A**) In the local cohort, RXRG expression was examined by qRT-PCR in 14 paired KIRC samples and adjacent normal tissues ($P < 0.01$). (**B**) The TCGA cohort contained 541 tumor samples and 72 normal tissue samples ($P < 0.01$)

Table 1 The relationship between RXRG expression and clinicopathological features in the TCGA cohort

Clinicopathological features	Low expression of RXRG ($n=270$)	High expression of RXRG ($n=271$)	*P* value
Race, n (%)			0.668
Asian & Black or African American	34 (6.4%)	31 (5.8%)	
White	232 (43.4%)	237 (44.4%)	
Gender, n (%)			0.062
Female	83 (15.3%)	104 (19.2%)	
Male	187 (34.6%)	167 (30.9%)	
Age, n (%)			0.898
<= 60	135 (25%)	134 (24.8%)	
> 60	135 (25%)	137 (25.3%)	
Pathologic T stage, n (%)			< 0.001
T1	118 (21.8%)	161 (29.8%)	
T2	45 (8.3%)	26 (4.8%)	
T3&T4	107 (19.8%)	84 (15.5%)	
Pathologic N stage, n (%)			0.185
N0	125 (48.4%)	117 (45.3%)	
N1	11 (4.3%)	5 (1.9%)	
Pathologic M stage, n (%)			0.066
M0	207 (40.7%)	222 (43.7%)	
M1	47 (9.3%)	32 (6.3%)	
Pathologic stage, n (%)			0.011
Stage I & Stage II	151 (28.1%)	181 (33.6%)	
Stage III & Stage IV	117 (21.7%)	89 (16.5%)	
Histologic grade, n (%)			0.003
G1&G2	108 (20.3%)	142 (26.6%)	
G3&G4	159 (29.8%)	124 (23.3%)	

CI = 1.898–3.743, $P < 0.001$), and RXRG expression (HR = 0.617, 95% CI = 0.457–0.834, $P = 0.002$) were significant variables for overall survival (OS) in KIRC (Table 2). Meanwhile, the significant variables for disease-free survival (DFS) in KIRC were pathologic T stage (HR = 5.606, 95% CI = 3.697–8.502, $P < 0.001$), pathologic N stage (HR = 3.864, 95% CI = 1.831–8.157, $P < 0.001$), pathologic M stage (HR = 9.219, 95% CI = 6.294–13.504, $P < 0.001$), histologic grade (HR = 4.850, 95% CI = 2.925–8.043, $P < 0.001$), and RXRG expression (HR = 0.492, 95% CI = 0.333–0.729, $P < 0.001$) (Table 2). The KM curves showed that low RXRG expression was significantly associated with worse OS and DFS in KIRC patients (Fig. 2A and B). The data analysis results from E-MTAB-1980 dataset also demonstrated the same trend, showing that low RXRG expression was significantly associated with worse OS ($P = 0.018$, Supplementary Fig. 1). Moreover, time-dependent receiver operator characteristic (time-ROC) curves demonstrated a protective prognostic value of RXRG, with the area under the curve (AUC) values of 0.398 for OS and 0.402 for DFS (Fig. 2C and D). Taken together, these results indicate that RXRG may be a potential prognostic biomarker for KIRC.

Table 2 Univariate Cox regression analyses for prognosis in KIRC

Clinicopathological features	OS	*P* value	DFS	*P* value
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
Race				
Asian & Black or African American	Reference		Reference	
White	1.233 (0.685–2.221)	0.485	1.378 (0.640–2.970)	0.413
Gender				
Female	Reference		Reference	
Male	0.924 (0.679–1.257)	0.613	1.183 (0.786–1.781)	0.420
Age				
<= 60	Reference		Reference	
> 60	1.791 (1.319–2.432)	< 0.001	1.351 (0.926–1.971)	0.118
Pathologic T stage				
T1 & T2	Reference		Reference	
T3 & T4	3.210 (2.373–4.342)	< 0.001	5.606 (3.697–8.502)	< 0.001
Pathologic N stage				
N0	Reference		Reference	
N1	3.422 (1.817–6.446)	< 0.001	3.864 (1.831–8.157)	< 0.001
Pathologic M stage				
M0	Reference		Reference	
M1	4.401 (3.226–6.002)	< 0.001	9.219 (6.294–13.504)	< 0.001
Histologic grade				
G1&G2	Reference		Reference	
G3&G4	2.665 (1.898–3.743)	< 0.001	4.850 (2.925–8.043)	< 0.001
RXRG expression				
Low	Reference		Reference	
High	0.617 (0.457–0.834)	0.002	0.492 (0.333–0.729)	< 0.001

RXRG-related differentially expressed genes and bioinformatic analyses

The RXRG-related differentially expressed genes (DEGs) were investigated between low and high RXRG expression groups. A total of 3,778 genes were obtained by excluding the genes with $P > 0.0001$. GO and KEGG analyses were performed to determine the biological processes involved in KIRC tumorigenesis. The results of the GO term analyses revealed that the genes are involved in the following: (1) biological processes, including acute inflammatory response, endothelium development, and endothelial cell differentiation; (2) cellular components, such as collagen-containing extracellular matrix, vesicle lumen, and

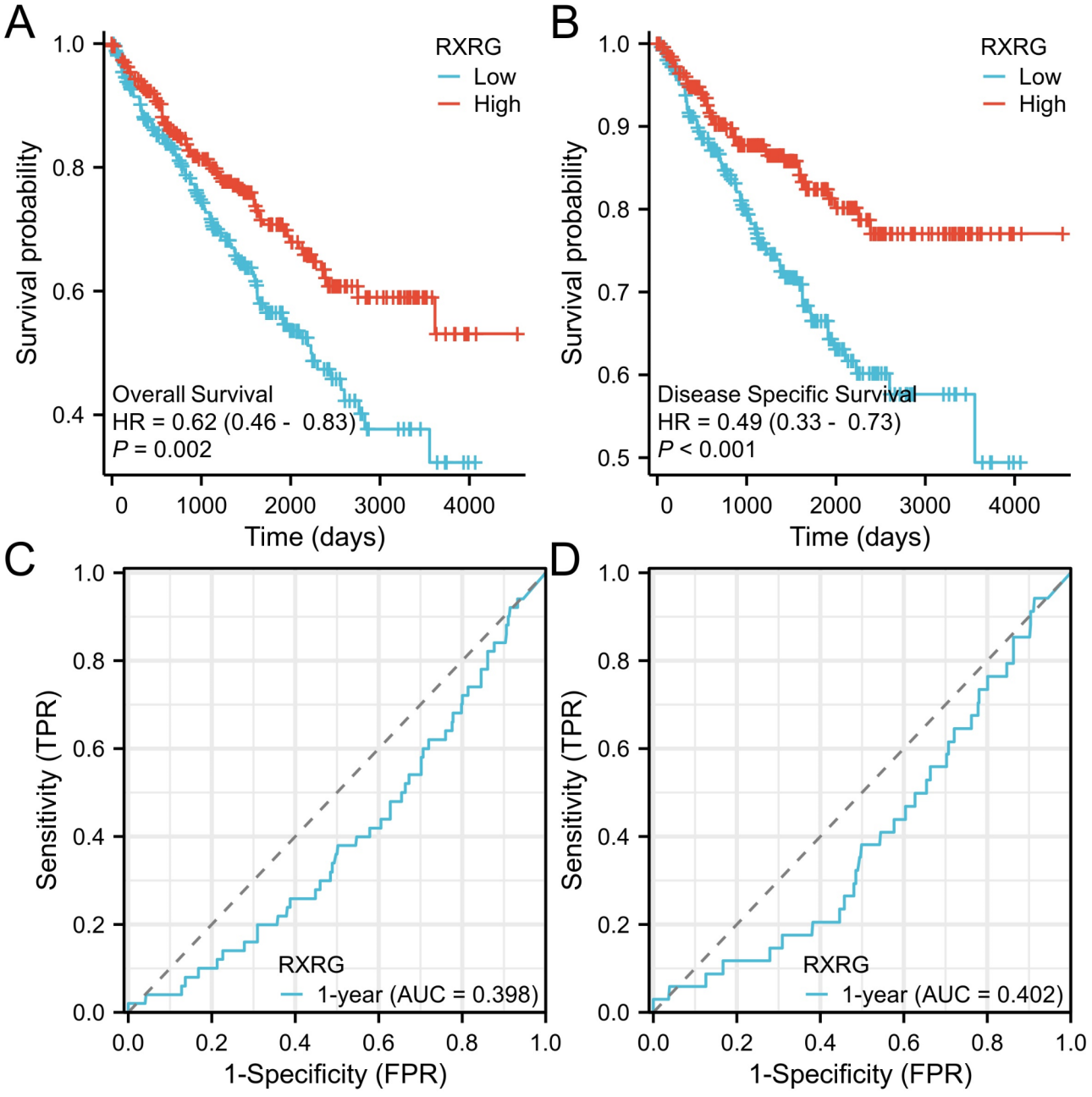

Fig. 2 Low RXRG expression was associated with worse prognosis in KIRC. Notes: (**A**) Low RXRG expression was significantly associated with worse OS of KIRC patients ($P = 0.002$). (**B**) Low RXRG expression was significantly associated with worse DFS of KIRC patients ($P < 0.001$). (**C**) time-ROC curve for RXRG expression in OS of KIRC patients (AUC = 0.398). (**D**) time-ROC curve for RXRG expression in DFS of KIRC patients (AUC = 0.402)

cytoplasmic vesicle lumen; and (3) molecular functions, such as enzyme inhibitor activity, peptidase inhibitor activity, and endopeptidase inhibitor activity (Table 3). The results of the KEGG pathway analyses showed that RXRG participated in the functional regulation of several signaling pathways (Table 3). As the most enriched pathway, the protein interactions of genes enriched in "Transcriptional misregulation in cancer" were investigated by PPI analyses (Fig. 3). The top ten hub genes in "Transcriptional misregulation in cancer" were further analyzed (Fig. 4). According to the TCGA database, the results of Pearson's correlation analyses demonstrated that RUNX2, CEBPB, and MMP9 exhibited a potential negative correlation with RXRG expression, whereas NFKB1 exhibited a possible positive correlation with RXRG ($P < 0.05$). However, no significant correlation was found between RXRG expression and H3C12, H3C13, SPL1, CEBPA, IL6, or RUNX1 ($P > 0.05$).

According to the GSEA analysis, we found these DEGs were involved in senescence-related pathways (Supplementary Table 2). In the low expression area of RXRG, the enrichment scores of these pathways reached the lowest levels (Supplementary Fig. 2).

The relationship between RXRG expression and tumor immune infiltration in KIRC

The findings from the immune infiltration analyses suggest a correlation between RXRG expression and immune infiltration patterns in KIRC. The results indicate a significant relationship between RXRG expression levels and various immune cell populations, including macrophages, Treg, dendritic cells, neutrophils, Th17 cells, Tem, T helper cells, NK CD56dim cells, Tgd, Mast cells, CD8 T cells, and NK cells (Fig. 5A). Specifically, there was a positive association between RXRG expression and NK cells, while a negative association was observed with macrophages (Fig. 5B and C). Furthermore, the enrichment score for NK cells was significantly higher in the high RXRG expression group compared to the low RXRG expression group, whereas the enrichment score for macrophages was significantly lower in the high RXRG expression group (Fig. 5D, $P < 0.001$). These results suggest that RXRG expression may influence KIRC tumorigenesis by modulating immune infiltration within the tumor microenvironment.

Table 3 The top 5 most significant item of GO and KEGG analyses of the DEGs of RXRG in KIRC

Category	Term	Count	*P*value
Biological processes	GO:0002526 acute inflammatory response	53	1.9795E-12
	GO:0003158 endothelium development	54	1.0493E-09
	GO:0045446 endothelial cell differentiation	49	1.7696E-09
	GO:0006953 acute-phase response	27	3.4707E-09
	GO:0010466 negative regulation of peptidase activity	84	3.0086E-08
Cellular components	GO:0062023 collagen-containing extracellular matrix	140	4.5996E-13
	GO:0031983 vesicle lumen	112	3.3025E-12
	GO:0060205 cytoplasmic vesicle lumen	111	5.0586E-12
	GO:0034774 secretory granule lumen	110	6.2054E-12
	GO:0005788 endoplasmic reticulum lumen	105	4.1311E-11
Molecular functional	GO:0004857 enzyme inhibitor activity	122	2.5599E-09
	GO:0030414 peptidase inhibitor activity	67	3.6757E-08
	GO:0004866 endopeptidase inhibitor activity	65	4.1428E-08
	GO:0061135 endopeptidase regulator activity	67	1.8356E-07
	GO:0005178integrin binding	56	4.367E-07
KEGG pathways	Complement and coagulation cascades	37	0.00012538
	Transcriptional misregulation in cancer	61	0.00049868
	Axon guidance	56	0.00059401
	Lysosome	43	0.00098402
	Mineral absorption	23	0.00117849

Discussion

Renal cell carcinoma, a prevalent urological malignancy, poses a significant burden on patients globally [2, 3]. KIRC is the most common subtype of RCC, characterized by remarkable heterogeneity and metastatic capacity [17, 19]. Despite the progress of early diagnosis and individualized treatment, which has improved the survival of KIRC patients recently [5, 7], the prognosis of KIRC patients with advanced clinical stages remains unsatisfactory. Therefore, identifying potential prognostic biomarkers could help clinicians in selecting optimal treatment strategies. To our knowledge, this is the first research to comprehensively assess the gene expression, functional implications, and prognostic value of RXRG in KIRC by integrating data from bioinformatics analysis and clinical tumor sample validation.

RXRG has been implicated in the progression of various diseases. The single nucleotide polymorphism of RXRG rs3753898 may correlate with genetic susceptibility to type 2 diabetes [20]. Moreover, RXRG may co-express with genes linked to psychiatric disorders and could influence intercellular signaling in the striatum [21]. Besides, aberrant RXRG expression has also been linked to several cancer types. In thyroid cancer, RXRG overexpression has been shown to promote tumor cell dedifferentiation and lymph node metastasis [16, 22]. Conversely, low RXRG expression could provide mechanistic benefits for transformed cells to acquire resistance to hallmarks of apoptosis in epithelial ovarian cancer [13]. In non-small cell lung cancer (NSCLC), RXRG methylation status significantly associated with worse survival of never-smokers in NSCLC [15]. In breast cancer, high RXRG expression was an independent predictor of longer cancer-specific survival and distant metastasis-free survival in estrogen receptor-positive patients [14]. However, the role of RXRG in KIRC tumorigenesis remains unclear and needs to be further studied.

In the present study, we first report that RXRG may serve as a novel prognostic factor in KIRC. The expression of RXRG was verified using qRT-PCR detection and TCGA RNA-Seq data, which indicated

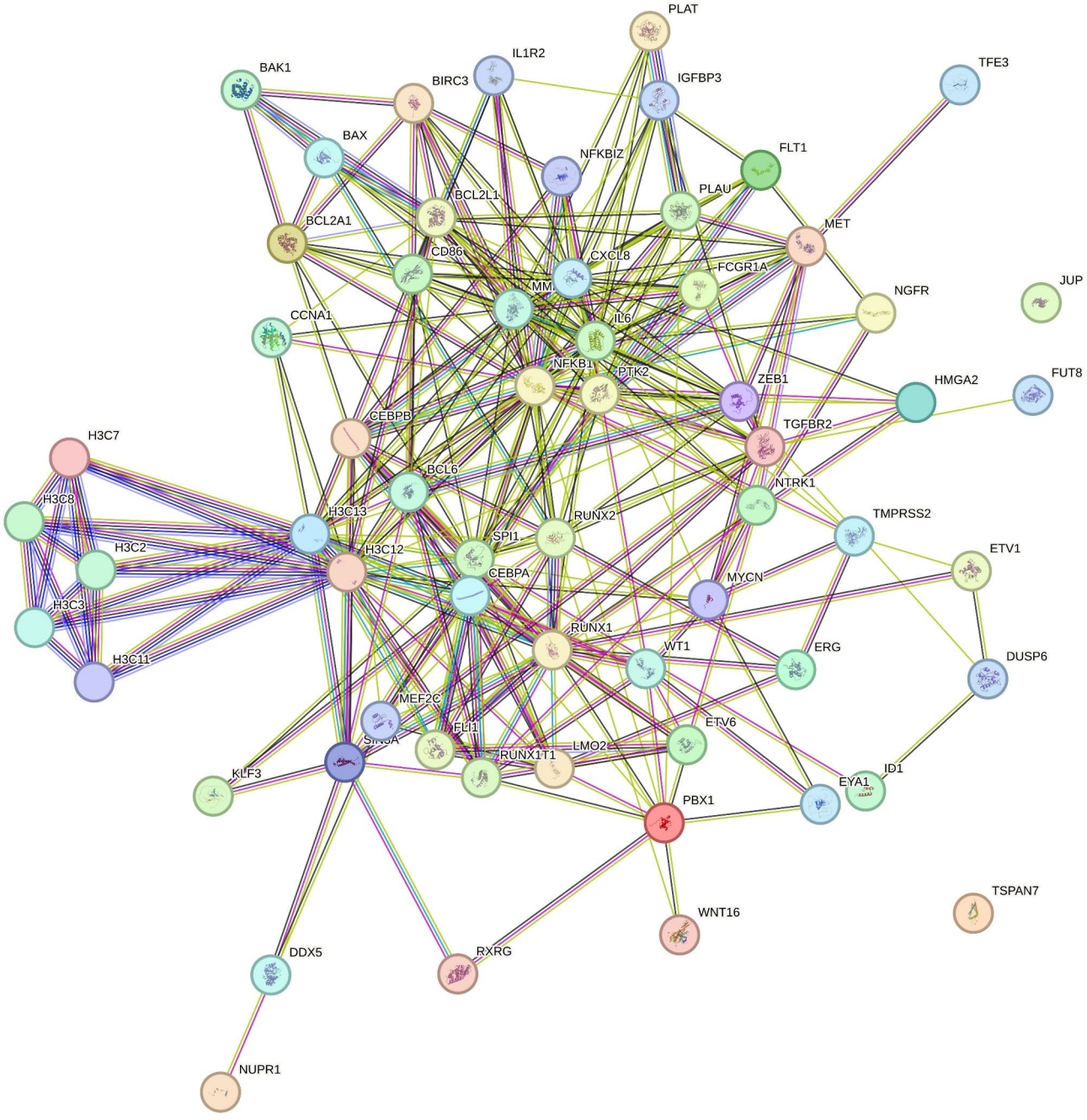

Fig. 3 Network of protein–protein interaction (PPI) analyses of RXRG-related differentially expressed genes in KIRC

a significant downregulation of RXRG in KIRC tumor tissues compared to normal kidney tissues. In addition, this downregulation of RXRG was found to be correlated with unfavorable clinicopathological features, such as large tumor size, high clinical stage, and advanced histologic grade. Cox regression analyses and time-dependent ROC curves demonstrated that high RXRG expression was a protective factor for both OS and DFS in KIRC patients. KM curves also illustrated a significant association between high RXRG expression and a favorable prognosis in KIRC patients. These results provide strong evidence that RXRG acts as a tumor suppressor gene in KIRC.

The potential molecular mechanisms of RXRG in KIRC were also preliminarily evaluated in our research. GO and KEGG analyses were used to confirm the enrichment of RXRG-related DEGs in KIRC patients. The results of GO analyses suggested that the DEGs participate in various biological processes, cellular components, and molecular functions. In KEGG

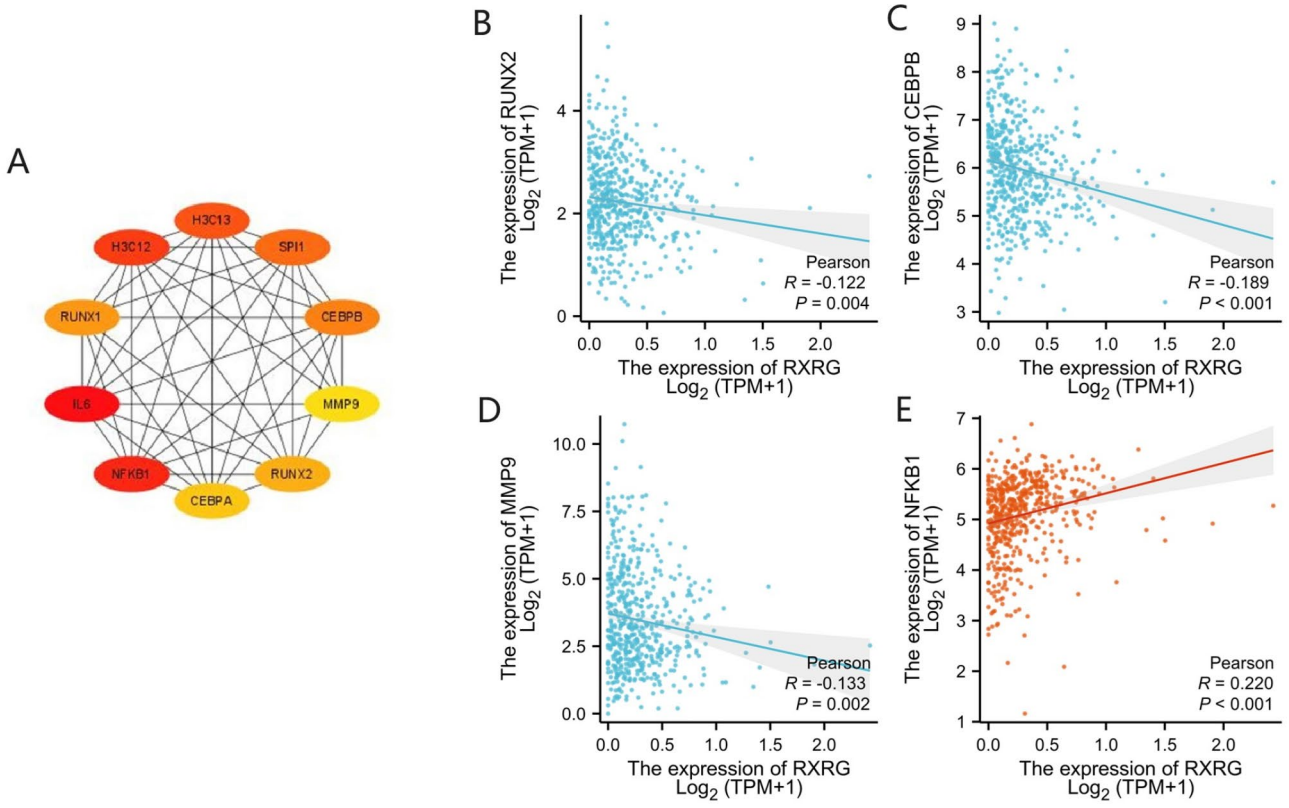

Fig. 4 The relationship between RXRG expression and hub genes in pathway of "Transcriptional misregulation in cancer". Notes: (**A**) The top ten hub genes in pathway of "Transcriptional misregulation in cancer". (**B** to **D**) RXRG expression was negatively correlated with RUNX2, CEBPB, and MMP9. (E) RXRG expression was positively correlated with NFKB1

analyses, the DEGs were found to be engaged in a series of signaling pathways crucial for cancer progression and metabolism. RXRG may participate the pathway of "Transcriptional misregulation in cancer" by regulating the expression of RUNX2, CEBPB, MMP9, and NFKB1.

In investigating the correlation between RXRG expression and tumor immune infiltration levels in KIRC, a significant association was found between RXRG expression and NK cells and macrophages. Previous research has demonstrated that higher levels of NK cells can enhance the innate immune response against tumor development, leading to improved prognoses for cancer patients [23]. Additionally, elevated levels of TRAF2 have been linked to the polarization of M2 macrophages, which can contribute to the progression, migration, and angiogenesis of KIRC through an autophagy-dependent pathway [24]. These findings suggest that RXRG may play a role in modulating the immune response to malignancies, though further research is needed to elucidate the underlying mechanisms.

Despite the substantial findings, this research still includes some limitations. First, the findings are mainly derived from multiple online databases and need to be validated through in vitro and in vivo experiments. Second, the prospect of RXRG in KIRC immunotherapy and molecular targeted therapy warrants further exploration.

In conclusion, RXRG expression was downregulated in KIRC tissues. The low expression of RXRG is associated with an increased risk of poor prognosis in KIRC. RXRG may function as a novel tumor suppressor gene by regulating cancer transcription and metabolism.

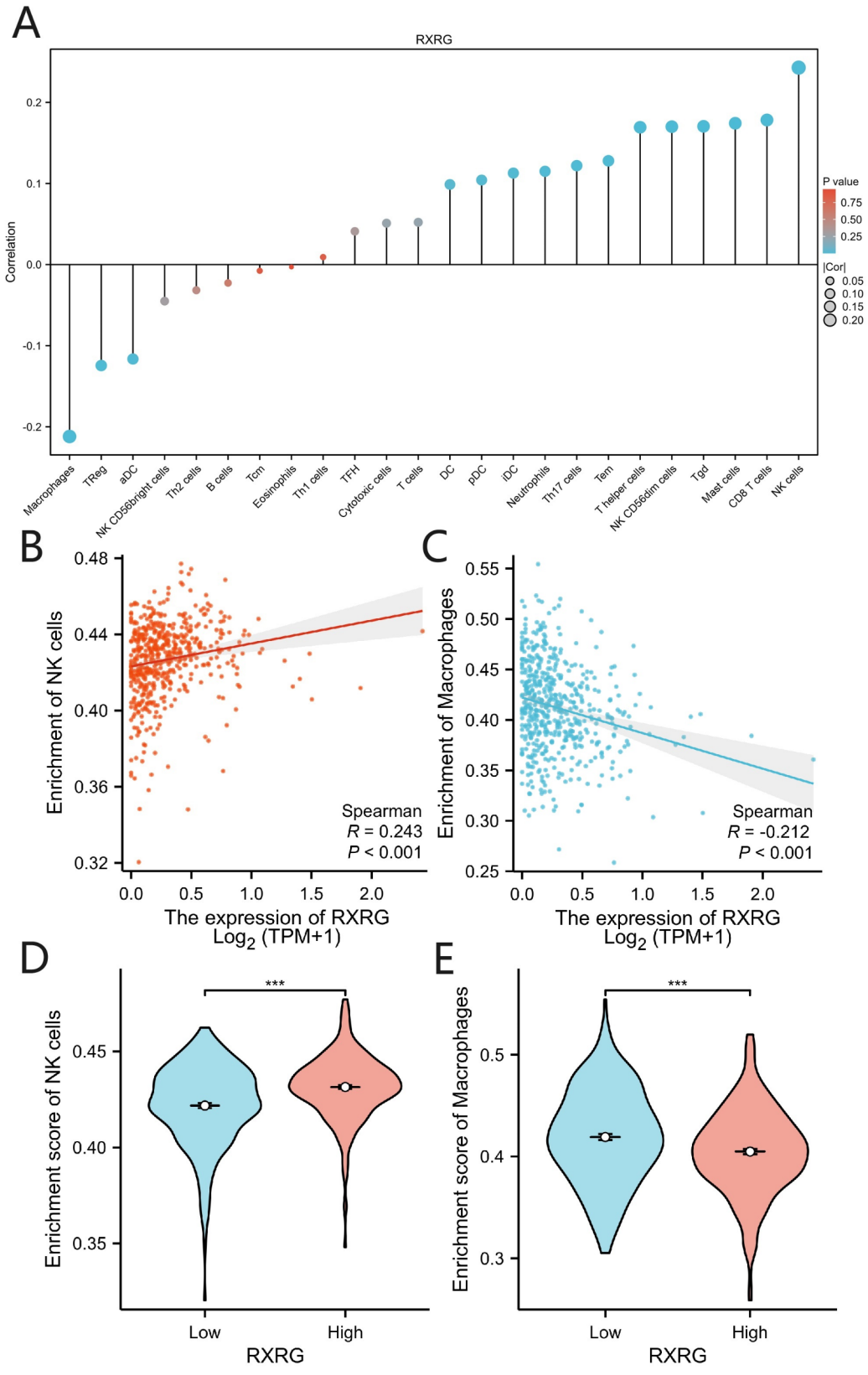

Fig. 5 Relationship between RXRG expression and immune infiltration in KIRC microenvironment. Notes: (**A**) Correlation between the relative abundance of 24 immune cells and RXRG expression. The size of the dots indicates the absolute value of Spearman's correlation coefficient R. (**B** and **C**) Correlation between RXRG expression and infiltration levels of NK cells, and macrophages. (**D** and **E**) Correlation between high and low RXRG expression and the infiltration levels of NK cells, and macrophages. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$

Abbreviations

AUC	Area under the curve
DEGs	Differentially expressed genes
DFS	Disease-free survival
DM	Distant metastasis
GEO	Gene Expression Omnibus
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
KIRC	Kidney clear cell carcinoma
LNM	Lymph node metastasis
OS	Overall survival
PPI	Protein-protein interaction
qRT-PCR	Quantitative real-time polymerase chain reaction
RARs	Retinoic acid receptors
RCC	Renal cell carcinoma
RXRG	Retinoid X receptory
RXRs	Retinoid X receptors
TCGA	The Cancer Genome Atlas
time-ROC	time-dependent receiver operator characteristic curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12894-025-01744-4.

Supplementary Material 1

Acknowledgements
This work was supported by a grant from the Wenzhou Science and Technology Project (No. Y20210176).

Author contributions
Jianda Dong designed this work. Lailai Fan collected the samples and performed experiments. Qiaolin Wu participated in the drawing of charts and figures. Zhouci Zheng performed all the bioinformatical analyses and wrote the manuscript. All authors reviewed the manuscript.

Funding
This work was supported by a grant from the Wenzhou Science and Technology Project (No. Y20210176).

Data availability
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was proved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 25 June 2024 / Accepted: 14 March 2025
Published online: 28 March 2025

References

1. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015;67(3):519–30.
2. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl). 2022;135(5):584–90.
3. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
4. Wei JH, Feng ZH, Cao Y, Zhao HW, Chen ZH, Liao B, et al. Predictive value of single-nucleotide polymorphism signature for recurrence in localised renal cell carcinoma: a retrospective analysis and multicentre validation study. Lancet Oncol. 2019;20(4):591–600.
5. Sanchez-Gastaldo A, Kempf E, Gonzalez Del Alba A, Duran I. Systemic treatment of renal cell cancer: a comprehensive review. Cancer Treat Rev. 2017;60:77–89.
6. He Y, Luo Y, Huang L, Zhang D, Wang X, Ji J, et al. New frontiers against sorafenib resistance in renal cell carcinoma: from molecular mechanisms to predictive biomarkers. Pharmacol Res. 2021;170:105732.
7. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med. 2017;376(4):354–66.
8. Liu D, Shu G, Jin F, Qi J, Xu X, Du Y et al. ROS-responsive chitosan-SS31 prodrug for AKI therapy via rapid distribution in the kidney and long-term retention in the renal tubule. Sci Adv. 2020;6(41).
9. Pfahl M, Chytil F. Regulation of metabolism by retinoic acid and its nuclear receptors. Annu Rev Nutr. 1996;16:257–83.
10. Dawson MI, Xia Z. The retinoid X receptors and their ligands. Biochim Biophys Acta. 2012;1821(1):21–56.
11. Tang XH, Gudas LJ. Retinoids, retinoic acid receptors, and cancer. Annu Rev Pathol. 2011;6:345–64.
12. Conzen SD. Minireview: nuclear receptors and breast cancer. Mol Endocrinol. 2008;22(10):2215–28.
13. Kalra RS, Bapat SA. Expression proteomics predicts loss of RXR-gamma during progression of epithelial ovarian cancer. PLoS ONE. 2013;8(8):e70398.
14. Joseph C, Al-Izzi S, Alsaleem M, Kurozumi S, Toss MS, Arshad M, et al. Retinoid X receptor gamma (RXRG) is an independent prognostic biomarker in ER-positive invasive breast cancer. Br J Cancer. 2019;121(9):776–85.
15. Lee SM, Lee JY, Choi JE, Lee SY, Park JY, Kim DS. Epigenetic inactivation of retinoid X receptor genes in non-small cell lung cancer and the relationship with clinicopathologic features. Cancer Genet Cytogenet. 2010;197(1):39–45.
16. Liu Z, Zhou G, Nakamura M, Bai Y, Li Y, Ozaki T, et al. Retinoid X receptor gamma up-regulation is correlated with dedifferentiation of tumor cells and lymph node metastasis in papillary thyroid carcinoma. Pathol Int. 2011;61(3):109–15.
17. Sato Y, Yoshizato T, Shiraishi Y, Maekawa S, Okuno Y, Kamura T, et al. Integrated molecular analysis of clear-cell renal cell carcinoma. Nat Genet. 2013;45(8):860–7.
18. Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, et al. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res. 2021;49(D1):D605–12.
19. Chen W, Pan X, Zhou W, Xu D, Chen J, Dong K et al. Microbiome subsets determine tumor prognosis and molecular characteristics of clear-cell renal cell carcinoma: a multi-center integrated analysis of microbiome, metabolome, and transcriptome data. Front Med. 2023.
20. Yu H, Wang S, Hu W, Xu L, Ding Y, Kong D, et al. Association between single-nucleotide polymorphisms of RXRG and genetic susceptibility to type 2 diabetes in South China. Curr Mol Med. 2020;20(6):408–14.
21. Ashbrook DG, Williams RW, Lu L, Hager R. A cross-species genetic analysis identifies candidate genes for mouse anxiety and human bipolar disorder. Front Behav Neurosci. 2015;9:171.
22. Schulten HJ, Al-Mansouri Z, Baghallab I, Bagatian N, Subhi O, Karim S, et al. Comparison of microarray expression profiles between follicular variant of papillary thyroid carcinomas and follicular adenomas of the thyroid. BMC Genomics. 2015;16(Suppl 1):S7.
23. Tang F, Li J, Qi L, Liu D, Bo Y, Qin S, et al. A pan-cancer single-cell panorama of human natural killer cells. Cell. 2023;186(19):4235–e5120.
24. Xu Y, Li L, Yang W, Zhang K, Zhang Z, Yu C, et al. TRAF2 promotes M2-polarized tumor-associated macrophage infiltration, angiogenesis and cancer progression by inhibiting autophagy in clear cell renal cell carcinoma. J Exp Clin Cancer Res. 2023;42(1):159.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.