A novel lncRNA-miRNA-mRNA competing endogenous RNA regulatory network in lung adenocarcinoma and kidney renal papillary cell carcinoma

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Abstract

Background: GPRIN1 may be a novel tumor regulator, but its role and mechanism in tumors are still unclear.

Methods: First, a pan-cancer correlation analysis was conducted on the expression and prognosis of GPRIN1 based on the data downloaded from The Cancer Genome Atlas (TCGA) database. Second, the Starbase database was used to predict the upstream miRNAs and lncRNAs of GPRIN1, and the expression analysis, survival analysis, and correlation analysis were performed to screen the microRNA (miRNAs)/long non-coding RNAs (lncRNAs) that had a correlation with kidney renal papillary cell carcinoma (KIRP) or lung adenocarcinoma (LUAD). Third, the CIBERSORT algorithm was employed to calculate the proportion of various types of immune cells, and then the R packages were used for evaluating the relation between GPRIN1 expression and tumor immune cell infiltration as well as between GPRIN1 and the immune cell biomarker. Finally, the correlation analysis was made on GPRIN1 and immune checkpoints (CD274, CTLA4, and PDCD1).

Results: The pan-cancer analysis suggested that GPRIN1 was up-expressed in KIRP and LUAD, and it correlated with poor prognosis. LINC00894/MMP25-AS1/SNHG1/LINC02298/MIR193BHG-miR-140-3p was likely to be the most promising upstream regulation pathway of GPRIN1. Upexpression of LINC00894/MMP25-AS1/SNHG1/LINC02298/MIR193BHG and downexpression of miR-140-3p were found relevant with poor outcomes of KIRP and LUAD. GPRIN1 expression was significantly correlated with tumor immune cell infiltration, immune cell biomarkers, and immune checkpoints.
Conclusions: The competitive endogenous (ceRNA) of miR-140-3p-GPRIN1 axis and its upstream lncRNAs are closely related to KIRP and LUAD, and might affect the prognosis and therapeutic effect of KIRP and LUAD.

**KEYWORDS**
competing endogenous RNAs, GPRIN1, Kidney renal papillary cell carcinoma, Lung adenocarcinoma, miR-140-3p

**INTRODUCTION**

The G protein regulated inducer of neurite outgrowth 1 (GPRIN1) is a protein coding gene. Diseases associated with GPRIN1 include cerebral creatine deficiency syndrome 2 and cerebral creatine deficiency syndrome, for which Methyl-CpG Binding Protein 2 (MECP2) and associated Rett syndrome are relatable pathways. Current studies of GPRIN1 are limited and insufficient. The Cancer Genome Atlas (TCGA) project has generated genomic, epigenomic, transcriptomic, and proteomic data for over 20 different cancer types [14–21]. These data sets provide broad insight into the underlying genetic aberrations existing across multiple cancer types. In addition, TCGA has clinical data describing specific metrics such as histopathology and clinical stage, among others. Overall, TCGA data has the potential for determining the critical genetic significance of genetic aberrations. Pan-cancer analysis of 33 tumors performed in this study based on the data from TCGA found that GPRIN1 was significantly overexpressed in a variety of tumors together with its correlation with prognosis. Thus, it has been speculated that GPRIN1 might be closely related to tumorigenesis.

In this study, expression analysis and survival analysis of GPRIN1 in various types of tumors were first performed. Then the upstream microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) of GPRIN1 were predicted to establish the competing endogenous RNAs (ceRNA) action network of lncRNA-miRNA-GPRIN1. Finally, assessment was made on the relationship between GPRIN1 and immune cell infiltration, immune cell markers, and immune checkpoints, respectively. GPRIN1 proved to associate with poor prognosis and tumor immune invasion of kidney renal papillary cell carcinoma (KIRP) or lung adenocarcinoma (LUAD).

**METHODS**

**Data collection, preprocessing, and analysis**

The RNA sequencing transcriptome data and clinical data of 33 cancer types were downloaded from TCGA database (https://portal.gdc.cancer.gov/). Perl script was used to organize the data. The Wilcoxon signed-rank test was utilized to identify differentially expressed genes by the limma package of R on account of the cutoff values: $|\text{Log2FC}| > 1$ and FDR $< 0.05$. The survival package of R was applied in identifying the prognostic gene. $p < 0.05$ was deemed as statistically significant.

**Prediction of upstream miRNA/lncRNA of GPRIN1**

The Starbase database was employed to predict miRNAs interacted with messenger RNA (mRNA) and lncRNAs acted with miRNA.

**GEPIA database analysis**

GEPIA (http://gepia.cancer-pku.cn/) was utilized for survival analysis and helped evaluate the correlation between GPRIN1 and immune checkpoint expression. $|R| > 0.1$ and $p < 0.05$ were set to identify selection criteria of statistical significance.

**TIMER database analysis**

TIMER (https://cistrome.shinyapps.io/timer/) was used to evaluate the correlation between genes and immune cells where $p < 0.05$ was considered to embody statistical significance.

**Statistical analysis**

The statistical analysis in this work was performed by R package or online database. $|\text{Log2FC}| > 1$ and $p < 0.05$ were considered to embody statistical significance.

**RESULTS**

**Pan-cancer analysis of GPRIN1**

In previous screening of tumorigenesis-related differential genes conducted by our research group, it was found that GPRIN1 was highly expressed in tumor tissues. The pan-cancer analysis suggested that the expression of GPRIN1 increased in 16 tumor types, that is, bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), KIRP, liver hepatocellular carcinoma (LIHC), LUAD, lung squamous cell carcinoma (LUSC),
prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC), and decreased in two tumor types, that is, glioblastoma multiforme (GMB) and kidney chromophobe (KICH) (Figure 1(a)). As shown in Figure 1(b), the expression of GPRIN1 in BLCA, BRCA, CHOL, ESCA, HNSC, KIRP, LUAD, LUSC, pancreatic adenocarcinoma (PAAD), STAD, and UCEC increased considerably, but it diminished significantly in GBM. Therefore, GPRIN1 showed an upregulation in BLCA, BRCA, CHOL, ESCA, HNSC, KIRP, LUAD, LUSC, pancreatic adenocarcinoma (PAAD), STAD, and UCEC increased considerably, but it diminished significantly in GBM. Therefore, GPRIN1 showed an upregulation in BLCA, BRCA, CHOL, ESCA, HNSC, KIRP, LUAD, LUSC, pancreatic adenocarcinoma (PAAD), STAD, and UCEC increased considerably, but it diminished significantly in GBM. 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Effect of GPRIN1 on the prognosis of tumor

Survival analysis on GPUIN1 was conducted in BLCA, BRCA, CHOL, ESCA, HNSC, KIRP, LUAD, LUSC, PAAD, STAD, UCEC, and GBM. As shown in Figure 2, the high expression in KIRP, LUAD, and LUSC was accompanied by poor prognosis, especially in KIRP and LUAD. Therefore, GPRIN1 might be a biomarker of poor prognosis in patients with KIRP and LUAD.

Predictive analysis of upstream miRNA of GPRIN1

The Starbase database was used for predicting upstream miRNAs that could regulate the expression of GPRIN1 (see Supporting Information Table S1). As there should be a negative correlation between miRNA and GPRIN1, the results of expression correlation analysis showed that six miRNAs were significantly negatively correlated with GPRIN1 in KIRP, and 13 miRNAs were negatively correlated with GPRIN1 in LUAD (Table 1). The survival analysis demonstrated that miR-140-3p, miR-140-5p, miR-181-5p, miR-185-5p, miR-362-3p, and miR-1270 all showed an inverse correlation with prognosis in KIRP. miR-181c-5p, miR-181d-5p, miR-23b-3p, miR-184, miR-181a-5p, miR-1287-5p, miR-140-3p, miR-362-3p, miR-335-5p, and miR-628-5p were negatively correlated with the prognosis in LUAD. miR-140-3p was found to be the upstream miRNA of GPRIN1 shared by KIRP and LUAD (Figure 3).

Predictive analysis of upstream lncRNAs of miR-140-3p

The Starbase database was also employed to predict the upstream lncRNA of miR-140-3p and identified a total of 135 lncRNAs. Referring to the regulation mechanism of ceRNA,
lncRNA should be negatively correlated with miRNA, but positively correlated with GPRIN1. The expression correlation analysis showed that LINC00894, MMP25-AS1, N4BP2L2-IT2, SNHG1, STAG3L5P-PVRIG2P-PILRB, TMEM147-AS1, and TUG1 showed a positive correlation with GPRIN1, and a negative correlation with miR-140-3p in KIRP (Table 2). In LUAD, MIR193BHG was positively correlated with GPRIN1 and negatively correlated with miR-140-3p. The survival analysis suggested that the high expression of LINC00894, MMP25-AS1, and SNHG1 might be the upstream potential lncRNAs of the miR140-3p/GPRIN1 axis in KIRP, and LINC02298 and MIR193BHG may be the upstream potential lncRNAs of the miR140-3p/GPRIN1 axis in LUAD.

**GPRIN1 and immune cell infiltration**

As shown in Figure 5, there were significant differences in activated memory CD4 T cells, γδ T cells, M0

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**TABLE 1 Correlation analysis between GPRIN1 and predicted miRNAs**

| Cancer | Gene   | miRNA    | Cor   | p value | logFC  | diffPval |
|--------|--------|----------|-------|---------|--------|----------|
| KIRP   | GPRIN1 | hsa-miR-140-3p | -0.37827 | 4.05E-11 | -0.01796 | 0.97316  |
| KIRP   | GPRIN1 | hsa-miR-185-5p | -0.3132  | 6.32E-08  | 0.978937  | 1.93E-10  |
| KIRP   | GPRIN1 | hsa-miR-362-3p | -0.30888  | 9.72E-08  | -1.04562  | 1.10E-08  |
| KIRP   | GPRIN1 | hsa-miR-140-5p | -0.2694  | 3.69E-06  | -0.65712  | 1.28E-07  |
| KIRP   | GPRIN1 | hsa-miR-1270 | -0.22944  | 8.28E-05  | 0.519935  | 0.007381  |
| KIRP   | GPRIN1 | hsa-miR-181a-5p | -0.21203  | 0.000292  | 0.277159  | 0.022883  |
| LUAD   | GPRIN1 | hsa-miR-181c-5p | -0.31979  | 1.64E-13  | 0.267642  | 0.028594  |
| LUAD   | GPRIN1 | hsa-miR-181d-5p | -0.22866  | 1.83E-07  | 0.646507  | 1.90E-06  |
| LUAD   | GPRIN1 | hsa-miR-23b-3p | -0.18826  | 1.87E-05  | 0.091887  | 0.173238  |
| LUAD   | GPRIN1 | hsa-miR-184 | -0.17819  | 5.02E-05  | -2.96043  | 7.92E-21  |
| LUAD   | GPRIN1 | hsa-miR-181a-5p | -0.16026  | 0.000276  | -0.0986  | 0.281727  |
| LUAD   | GPRIN1 | hsa-miR-1287-5p | -0.15835  | 0.000327  | 0.843028  | 3.76E-11  |
| LUAD   | GPRIN1 | hsa-miR-192-5p | -0.15139  | 0.000596  | 1.708925  | 1.61E-10  |
| LUAD   | GPRIN1 | hsa-miR-1913 | -0.14028  | 0.001462  | 0.049539  | 0.010832  |
| LUAD   | GPRIN1 | hsa-miR-140-3p | -0.12673  | 0.004099  | -1.11738  | 8.16E-21  |
| LUAD   | GPRIN1 | hsa-miR-215-5p | -0.12431  | 0.004873  | 0.854984  | 0.116452  |
| LUAD   | GPRIN1 | hsa-miR-362-3p | -0.1227  | 0.005434  | 0.182563  | 0.398877  |
| LUAD   | GPRIN1 | hsa-miR-335-5p | -0.12214  | 0.005677  | -0.21038  | 0.000161  |
| LUAD   | GPRIN1 | hsa-miR-628-5p | -0.11783  | 0.00764  | 1.321685  | 2.33E-12  |

**FIGURE 3** Survival analysis of miR-140-3p in KIRP (a) and LUAD (b)
macrophages, M2 macrophages, and mast cells resting between the high-expressed and low-expressed GPRIN1 groups in KIRP. There were considerable differences in plasma cells, activated memory CD4 T cells, regulatory T cells (Tregs), γδ T cells, M0 macrophages, M1 macrophages, and resting mast cells between the high-expressed

| Cancer | IncRNA   | Gene     | Cor    | p value | logFC | diffPval  |
|--------|----------|----------|--------|---------|-------|-----------|
| KIRP   | LINC02298| GPRIN1   | 0.111845 | 0.057587 | 6.18E-01 | 3.91E-06 |
|        | LINC00894| GPRIN1   | 0.142357 | 0.015501 | 3.89E-01 | 3.07E-06 |
|        | N4BP2L2-IT2| GPRIN1  | 0.151988 | 0.00972  | 2.45E-01 | 3.21E-05 |
|        | TUG1     | GPRIN1   | 0.276773 | 1.95E-06 | 1.39E-01 | 0.038204 |
|        | STAG3L5P-PVRIG2P-PILRB | GPRIN1 | 0.182572 | 0.001858 | 6.58E-01 | 9.15E-07 |
|        | MMP25-AS1| GPRIN1   | 0.32708  | 1.52E-08 | 0.74897  | 2.20E-13 |
|        | TMEM147-AS1| GPRIN1 | 0.202996 | 0.000529 | 2.92E-01 | 0.004841 |
|        | SNHG1    | GPRIN1   | 0.202845 | 0.000534 | 7.07E-01 | 3.36E-07 |
|        | OIP5-AS1 | GPRIN1   | 0.081594 | 0.166452 | 1.30E-01 | 0.032281 |
| LUAD   | LINC02298| GPRIN1   | -0.13682 | 0.09193  | 0.361085 | 3.22E-06 |
|        | MIR193BHG| GPRIN1   | 0.162016 | 0.000252 | 0.384463 | 7.34E-09 |
|        | SNHG1    | GPRIN1   | 0.036109 | 0.414764 | 1.309259 | 2.11E-27 |
|        | UBA6-AS1 | GPRIN1   | 0.083112 | 0.060226 | 0.40373  | 1.64E-22 |

**FIGURE 4** Expression analysis and survival analysis for upstream lncRNAs of miR-140-3p/GPRIN1 in KIRP/LUAD
and low-expressed GPRIN1 groups in LUAD. In KIRP, the expression of GPRIN1 proved to be negatively correlated with M0 macrophages, M2 macrophages, activated mast cells and monocytes, but positively correlation with mast cells resting, activated NK cells, and activated memory CD4 T cells. In LUAD, GPRIN1 was negatively correlated with resting mast cells, plasma cells, and γδ T cells, and was positively correlated with activated dendritic cells, M0 macrophages, M1 macrophages, activated mast cells, and activated memory CD4 T cells.

Correlation between GPRIN1 and expression of immune cell biomarkers

As shown in Table 3, GPRIN1 had a positive correlation with the biomarker expressions of B cells, CD8+ T cells, and M1 macrophages, and was negatively correlated with M2 macrophages in KIRP. In LUAD, GPRIN1 showed another positive correlation with CD8+ T cells, CD4+ T cells, M1 macrophages, and M2 macrophages, and negative correlation with B cells.

The relationship between GPRIN1 and immune checkpoints

PD1, PD-L1, and CTLA-4 are important immune checkpoints responsible for tumor immune escape. The relationship between GPRIN1 and PD1, PD-L1, and CTLA-4 was evaluated. As shown in Figure 6, significant positive correlations between GPRIN1 and PD1, PD-L1 and CTLA-4 were found.
DISCUSSION

With still no effective treatment for tumors, cancer remains one of the leading causes of human death worldwide. By elucidating the molecular mechanism relatable to tumors, it is possible that important clues for developing effective therapeutic targets or specific prognostic biomarkers may be sought out. Currently, studies have found that tumorigenesis concerns major molecules and signal pathways. In recent years, the wide application of bioinformatics has

| Cancer | Gene 1 | Immune cell | Gene | Cor  | p value  |
|--------|--------|-------------|------|------|----------|
| KIRP   | GPRIN1 | B cell      | CD19 | 0.017350544 | 0.768984828 |
|        | GPRIN1 | B cell      | CD79A | 0.049740982 | 0.399311108 |
|        | GPRIN1 | CD8 + T cell | CD8A | 0.073773018 | 0.211015282 |
|        | GPRIN1 | CD8 + T cell | CD8B | 0.018041304 | 0.759924831 |
|        | GPRIN1 | CD4 + T cell | CD4  | −0.12054548 | 0.040624999 |
|        | GPRIN1 | M1 macrophage | NOS2 | 0.080583662 | 0.171873699 |
|        | GPRIN1 | M1 macrophage | IRF5 | 0.121136101 | 0.039645399 |
|        | GPRIN1 | M1 macrophage | PTGS2 | 0.011511653 | 0.845413995 |
|        | GPRIN1 | M2 macrophage | CD163 | −0.149456111 | 0.011016356 |
|        | GPRIN1 | M2 macrophage | VSG4  | −0.098806328 | 0.093623328 |
|        | GPRIN1 | M2 macrophage | MS4A4A | −0.186454757 | 0.001476748 |
|        | GPRIN1 | Neutrophil   | CECAM8 | 0.082684786 | 0.160929833 |
|        | GPRIN1 | Neutrophil   | ITGAM | 0.039498071 | 0.503386444 |
|        | GPRIN1 | Neutrophil   | CCR7  | −0.008869268 | 0.880593827 |
|        | GPRIN1 | Dendritic cell | HLA-DPB1 | −0.190670366 | 0.001145572 |
|        | GPRIN1 | Dendritic cell | HLA-DQB1 | −0.14514378 | 0.013993436 |
|        | GPRIN1 | Dendritic cell | HLA-DRA  | −0.198481685 | 0.000750705 |
|        | GPRIN1 | Dendritic cell | HLA-DPA1 | −0.177619516 | 0.002472826 |
|        | GPRIN1 | Dendritic cell | CD1C  | 0.048246536 | 0.41386168 |
|        | GPRIN1 | Dendritic cell | NRP1  | 0.307573679 | 1.13E-07 |
|        | GPRIN1 | Dendritic cell | ITGAX  | −0.050524997 | 0.391914787 |
|        |        |             |       |       |          |
| LUAD   | GPRIN1 | B cell      | CD19  | −0.048904656 | 0.262731919 |
|        | GPRIN1 | B cell      | CD79A | −0.048021876 | 0.271504287 |
|        | GPRIN1 | CD8 + T cell | CD8A  | 0.095932559 | 0.027838374 |
|        | GPRIN1 | CD8 + T cell | CD8B  | 0.030342515 | 0.487306175 |
|        | GPRIN1 | CD4 + T cell | CD4   | 0.061879207 | 0.15689107 |
|        | GPRIN1 | M1 macrophage | NOS2 | 0.133319714 | 0.002199987 |
|        | GPRIN1 | M1 macrophage | IRF5  | 0.279212209 | 8.58E-13 |
|        | GPRIN1 | M1 macrophage | PTGS2 | 0.070376858 | 0.106869269 |
|        | GPRIN1 | M2 macrophage | CD163 | 0.116259273 | 0.00763458 |
|        | GPRIN1 | M2 macrophage | VSG4  | 0.07081396 | 0.104731688 |
|        | GPRIN1 | M2 macrophage | MS4A4A | 0.038235675 | 0.381367227 |
|        | GPRIN1 | Neutrophil   | CECAM8 | −0.120996573 | 0.00546827 |
|        | GPRIN1 | Neutrophil   | ITGAM  | 0.133700664 | 0.00213611 |
|        | GPRIN1 | Neutrophil   | CCR7  | −0.029815617 | 0.49490142 |
|        | GPRIN1 | Dendritic cell | HLA-DPB1 | −0.056058676 | 0.199919354 |
|        | GPRIN1 | Dendritic cell | HLA-DQB1 | 0.018598546 | 0.670318849 |
|        | GPRIN1 | Dendritic cell | HLA-DRA  | −0.026250274 | 0.547910733 |
|        | GPRIN1 | Dendritic cell | HLA-DPA1 | −0.00237809 | 0.956593502 |
|        | GPRIN1 | Dendritic cell | CD1C  | −0.109818668 | 0.01758213 |
|        | GPRIN1 | Dendritic cell | NRP1  | 0.093725112 | 0.031652503 |
|        | GPRIN1 | Dendritic cell | ITGAX  | 0.108966561 | 0.012430503 |
helped to find molecular pathways that are closely related to tumors. In this work, differentiated expression analysis was made on 33 types of tumors based on TCGA database, and GPRIN1 was proved to be significantly overexpressed in KIRP and LUAD with relation to poor prognosis.

It has been reported that lncRNA can regulate gene expression through the ceRNA mechanism. Ninety-one

**FIGURE 6** Correlation of GPRIN1 expression with PD-1, PD-L1, and CTLA-4 expression in KIRP and LUAD
upstream miRNAs were predicted to bind to GPRIN1 by using the Starbase database, and expression correlation and survival analysis have suggested that six miRNAs were relatable to better prognosis in KIRP. Ten miRNAs were associated with better prognosis in LUAD. It was reported that such miRNAs could act as tumor suppressors during tumorigenesis. mir-140-3p plays an inhibitory role in lung adenocarcinoma, non-small-cell lung cancer and lung squamous cell carcinoma.\(^7\) miR-185-5p could suppress tumor malignancy of lung adenocarcinoma,\(^8\) and function as a tumor suppressor in metastatic clear-cell renal carcinoma by targeting HIF-2\(\alpha\).\(^9\) Downregulation of IncRNA LUCAT1 could suppress the migration and invasion of bladder cancer by targeting miR-181c-5p.\(^8\) microRNA-181d-5p was proved to have tumor-suppressive effects on non-small-cell lung cancer through the CDKN3-mediated Akt signaling pathway.\(^7\) miR-23b-3p was significantly associated with the biomarkers of these infiltrating immune cells and Tumor-Node-Metastasis (TNM) stage of non-small-cell lung cancer.\(^10\) miR-140-3p was found to be related to various types of human tumors. The upstream regulation of long noncoding RNA LUCAT1 suppresses the migration and invasion of bladder cancer by targeting miR-181c-5p.\(^8\) microRNA-181d-5p was proved to have tumor-suppressive effects on non-small-cell lung cancer through the CDKN3-mediated Akt signaling pathway.\(^7\) The mechanism of GPRIN1 was defined and the regulatory network of LINC00894/MMP25-AS1/SNHG1/LINC02298/MIR193BHG-miR-140-3p-GPRIN1 was built. GPRIN1 also could affect the outcome of cancer treatment by affecting tumor immune cell infiltration and immune checkpoint expression. However, limitations still pervade as retrospective analysis collected data from public databases, which makes bias and inadequacy inevitable. Therefore, larger scales of prospective studies are needed to further verify the validity of the prognostic features.

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CONFLICT OF INTEREST

The authors report no competing interests in this work.

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