The clinical significance of UBE2C gene in progression of renal cell carcinoma

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Renal cell carcinoma (RCC), with high morbidity and mortality, is one of the top ten serious cancers. Due to limited therapies and little knowledge about the mechanism underlying RCC, overall survival of RCC patients is poor. UBE2C is a member of ubiquitin modification system and promotes carcinogenesis in cancer, but its role in RCC is unknown. Based on the TCGA (The Cancer Genome Atlas) data, UBE2C was over-expressed in a total of 525 RCC tissues and displayed higher expression in advanced tissues (stage IV vs stage I, p<0.05). RT-qPCR and IHC analysis confirmed over-expression of UBE2C in 90 of clinical RCC tissues. Further, UBE2C was associated with clinical factors including TNM stage, gender, and pathological stage. And higher UBE2C expression predicted shorter overall survival and progression-free survival. Both univariate and multivariate COX analysis suggested UBE2C as a critical gene in RCC. Then GO and KEGG analysis showed that cell cycle and DNA replication pathways were two top signaling pathways affected by UBE2C. In vitro assay showed that knockdown of UBE2C in 786-O cells inhibited proliferation and migration significantly. Therefore, this study proves that UBE2C is an important gene in RCC and is essential to proliferation and migration of RCC.

Key words: UBE2C; GO analysis; KEGG analysis; renal cell carcinoma.

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Contributions: LW; study design, draft review; ZC, data acquisition and analysis, manuscript drafting. Both authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Funding: This research was supported by Natural Science Foundation of Jiangxi Province (No.20192BAB205075 and No.20202BAB206119) and Health Commission of Jiangxi Province (No.20204518).

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval: Not applicable.
Introduction

Renal cell carcinoma (RCC) is a malignant disease and originates from renal parenchyma urinary tubule epithelial system. Among them, clear cell carcinomas make up about 70% of all RCC patients. The main therapy for RCC is resection with chemo-radiotherapy. But RCC is not so sensitive to radiotherapy or chemotheraphy. In recent years, target therapy has been used to treat RCC and about 20-40% of RCC patients could benefit from target therapy. However, long-term survival is not easily acquired. According to the latest report released by AACR in 2019, the five-year survival rate for patients with distant metastasis is only 12%. And about 16% of patients are diagnosed with distant metastasis. In addition, a total of 73,820 persons will be subjected to kidney cancer and about 14,000 will die. This is partially due to the ignorance of mechanism underlying RCC.

UBC2 (UBE2C) is a member of the ubiquitin coupling enzyme E2 family and interacts with specific E3 enzymes, which leads to degradation of substrate proteins. The substrate proteins of UBE2C are cell cycle-related proteins involved in regulation of cell mitosis. Recent studies indicated that UBE2C played an oncogenic role in several types of cancer. However, the abnormal expression of UBE2C caused chromosomal instability and participated in development and progression in gastric cancer. UBE2C is expressed abundantly in breast cancer, colon cancer, and liver cancer. And UBE2C was shown to be closely correlated with tumor stage, which suggests that UBE2C might be a new tumor marker and a promising therapeutic target in these tumors. However, the expression of UBE2C in RCC and its clinical value remain unclear. The cancer genome atlas (TCGA) database is a public database consisted of cancer genomics from over 20,000 cases of primary cancer and matched normal samples spanning 33 cancer types. The database contributes greatly to the research on elucidation of molecular mechanism underlying tumorigenesis.

In order to evaluate the clinical significance of UBE2C in RCC, we extracted the clinical information of RCC patients and UBE2C expression profile in RCC tissues from TCGA database. Then the relationship of UBE2C with pathological factors and prognoses of RCC patients was analyzed. And the potential process as well as signaling pathways were explored.

Materials and Methods

Bioinformatics analysis and TCGA mining

In order to analyze the differential expression levels of UBE2C in RCC and normal renal tissues, TCGA database was extracted. The mRNA expression level of UBE2C from a total of 525 cases of RCC and 72 cases of normal renal tissues was downloaded from the TCGA database. Then, RStudio (Version 1.1.442), a free and open-source data analysis software, was used to analyze the differential expression of UBE2C and to deduce the overall survival (OS) and disease-free survival (DFS) curves. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) were used in conjunction with DAVID 6.8 and Enrichment Map plug-in Cytoscape to visualize the significant pathways and differential expression genes (DEGs) in RCC.

RCC tissues and pathological information of patients

A total of 90 RCC tissues and matched normal tissues were retrospectively collected to perform RT-qPCR analysis. All the patients had received radical operation in our hospital from July 2006 to December 2010. The last follow-up time was August 2017. The pathologic diagnosis of all cases was renal clear cell carcinoma after operation. This study was approved by the Ethics Committee of First affiliated Hospital of Gannan Medical University and written consent was collected from all patients.

RT-qPCR

Total RNA of renal cancer tissues and matched normal tissues was extracted with Trizol (Invitrogen, USA) and treated with RNase-free DNase (Promega, USA). SYBR Green quantitative real-time PCR was performed by StepOne Real-Time PCR system (Applied Biosystems 7000, USA). Beta-actin was used as the internal control. Relative expression level of each gene was calculated by the 2^(-ΔΔCt) method, in which ΔΔCt = ΔCt (Target gene-CTBeta-actin) - Control group ΔCt (CT_target gene-CTBeta-actin).

Immunohistochemical analysis

Human tumor tissues were fixed in 4% paraformaldehyde, embedded in paraffin and sectioned as 5 μm. Each sectioned tissues were incubated with antibody against UBE2C (1:500, ab252940, Abcam, NY, USA) diluted with 0.01 M PBST buffer (0.01 M PBS, 0.001% Triton X-100) for 12 h at 44°C followed by HRP-conjugated secondary antibody (1:100, Beyotime, Shanghai, China). Peroxidase conjugates were determined using 3,3′-diaminobenzidine solution.

RNA interference assay (RNAi)

siRNA fragments targeting human UBE2C gene (siUBE2C: 5'-TCTTTTGTGGATTTCTGTATAG-3') was designed and synthesized. Random sequence was designed as negative control (NC). Then RCC typical cells 786-O cells were cultured in a 6-well plate and transduced with siUBE2C or NC (General Biosystems, Anhui, China) by Lipofectamine (Yeasen, Shanghai, China) for 4-6 h according to the manufacturer’s instruction. The knockdown efficiency of siUBE2C was tested by RT-qPCR method.

Cell proliferation assay

Treated cells were seeded into a 96-well plate at 5×10^3 cell/well and cultured consecutively for 96 h. At each designed time point, 10 µL of CCK-8 agent was added and cultured for another 1-2 h. Then OD value at 450 nm was detected on microplate reader (Molecular Devices, CA, USA). The proliferation rate of cells was calculated according to the negative control.

Cell invasion assay

Transwell rooms with 8-µm-pore size membrane were pre-treated with 0.2 mL Matrigel 12 h before seeding tumor cells. Then a total of 2×10^4 cells/well was seeded into upper room and DMEM medium without FBS was added. DMEM medium containing 15% FBS was added in the lower room. After culture for 24 h, cells on the upper room were removed and cells in the lower surface of upper room were fixed by 4% paraformaldehyde for 30 min and dyed with 0.5% crystal violet for 10 min. Then stained cells were observed under a microscope and counted.

Statistical analysis

SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA) was used to analyze the experimental data. All data was expressed as mean±SD. TCGA data were analyzed by the independent samples t-test to compare the differential levels of UBE2C mRNA between RCC and control. Chi-square test or Fisher’s exact test was employed to analyze the relationship between UBE2C expression and clinicopathological factors of RCC patients. Kaplan-Meier analysis was used to produce the survival curve. Univariate and Cox multivariate survival analyses were performed to analyze the prognostic significance of UBE2C in RCC patients. The difference was considered statistically significant when the p-value was less than 0.05.
Results

UBE2C was highly expressed in RCC

To explore the role of UBE2C in RCC, a total of 525 RCC cases and 72 normal cases from TCGA database (https://cancergenome.nih.gov/) were extracted for further analysis. The clinical information of the 525 RCC cases was displayed in Table 1. In brief, 187 cases were diagnosed as T3/T4 stage, accounted for 35.62% of total patients. About 205 cases were in stage III/IV, accounted for 39.05%. And 157 cases were dead, accounted for 29.9%. The mRNA level of UBE2C was significantly higher in RCC tissues than the control (p<0.05) (Figure 1A). The mean level of UBE2C in RCC was 5 folds of that in normal control. Furthermore, the expression level of UBE2C in stage IV patients was remarkably higher than that in stage I patients (Figure 1B).

To verify the bioinformatics data, the mRNA expression of UBE2C in 90 of RCC tissues and matched control was determined by RT-qPCR method. In consistency, UBE2C was expressed much higher in tumor tissues than the control and immunohistochemical (IHC) analysis confirmed this result (Figure 1C and 1D). Therefore, UBE2C was over-expressed in RCC tissues.

| Covariates | Type | Stat |
|------------|------|------|
| T          | T1   | 269(51.24%) |
| T2         | 69(13.14%) |
| T3         | 176(33.52%) |
| T4         | 11(2.1%) |
| N          | N0   | 238(45.33%) |
| N1         | 15(2.86%) |
| NX         | 272(51.81%) |
| M          | M0   | 419(79.81%) |
| M1         | 77(14.67%) |
| MX         | 29(5.52%) |
| Stage      | Stage I | 263(50.1%) |
|            | Stage II | 57(10.86%) |
|            | Stage III | 123(23.43%) |
|            | Stage IV | 82(15.62%) |
| Fustat     | Alive (0) | 368(70.1%) |
|            | Dead (1)  | 157(29.9%) |
| Age        | <=60 | 260(49.52%) |
|            | >60  | 265(50.48%) |

T1-4, primary tumor; N0, no regional lymph node involved; N1, few regional lymph nodes involved; NX, regional lymph node unevaluated; M0, no distant metastasis; M1, distant metastasis; MX, distant metastasis unevaluated; the percentage in parentheses means the number in the total cases; fustat is a parameter in survival analysis: fustat 1 indicated alive, fustat 0 indicated dead.

Figure 1. UBE2C was over-expressed in RCC. A) Expression profiles of UBE2C extracted from TCGA database. B) The expression of UBE2C in RCC patients with different pathological stage. C) The mRNA level of UBE2C in a total of 90 RCC tissues and adjacent normal control by RT-qPCR assay. D) The IHC analysis of UBE2C expression in RCC tissues and matched control; *p<0.05 was considered as statistically significant.
**Table 2.** Correlation analysis of UBE2C expression with clinical parameters of RCC patients based on TCGA data.

| Covariates | Type | Count | Low       | High      | p       |
|------------|------|-------|-----------|-----------|---------|
| Fustat     | Alive (0) | 368(70.1%) | 216(62.13%) | 152(50.02%) | 2.87E-09 |
|            | Dead (1)   | 157(29.9%) | 47(17.87%)  | 110(41.98%) | 8.33E-10 |
| Gender     | Female | 184(35.05%) | 107(40.86%) | 77(29.39%) | 0.008775808 |
|            | Male    | 341(64.95%) | 167(63.5%)  | 110(41.98%) | 8.33E-10 |
| T          | T1     | 269(51.24%) | 167(63.5%)  | 102(38.93%) | 6.83E-10 |
|            | T2     | 69(13.14%)  | 38(14.45%)  | 31(11.33%)  | 0.009062443 |
|            | T3     | 176(33.52%) | 57(21.67%)  | 119(45.42%) | 6.83E-10 |
|            | T4     | 272(51.81%) | 167(63.5%)  | 102(38.93%) | 6.83E-10 |
| N          | N0     | 238(45.33%) | 167(63.5%)  | 102(38.93%) | 6.83E-10 |
|            | N1     | 15(2.89%)   | 2(0.76%)    | 13(4.90%)   | 0.008775808 |
|            | N2     | 272(51.81%) | 167(63.5%)  | 102(38.93%) | 6.83E-10 |
| M          | M0     | 419(79.81%) | 226(55.93%) | 193(73.66%) | 2.88E-08 |
|            | M1     | 77(14.56%)  | 10(2.60%)   | 67(25.23%)  | 0.009062443 |
|            | M2     | 27(5.52%)   | 7(1.67%)    | 20(7.69%)   | 2.88E-08 |
| Stage      | Stage I | 263(50.1%) | 164(62.36%) | 99(37.78%) | 5.32E-11 |
|            | Stage II | 57(10.86%) | 34(12.93%)  | 23(8.71%)   | 5.32E-11 |
|            | Stage III | 123(23.43%) | 47(17.87%) | 76(29.01%) | 5.32E-11 |
|            | Stage IV | 82(15.62%) | 18(6.84%)   | 64(24.43%)  | 5.32E-11 |
| Age        | <=60 | 265(50.48%) | 132(50.19%) | 128(48.65%) | 0.826927487 |
|            | <60  | 265(50.48%) | 132(50.19%) | 128(48.65%) | 0.826927487 |

The percentage in the parentheses means the number in the total cases or in each group; p-value less than 0.05 displays significant correlation of UBE2C expression with clinical factor.

**Table 3.** Univariate COX analysis of 525 RCC patients from TCGA database.

| Term       | HR (lower 0.95) | HR (upper 0.95) | p-value |
|------------|-----------------|-----------------|---------|
| Gender     | 0.945597502     | 1.083103292     | 1.308059635 | 0.735990786 |
| T          | 2.031350134     | 2.725231486     | 2.442008372 | 6.27E-16 |
| N          | 0.657947058     | 0.783929498     | 1.018257165 | 0.802280687 |
| M          | 2.483956418     | 1.930133225     | 3.196099873 | 1.58E-12 |
| Stage      | 1.95621786     | 1.72032614      | 2.247889771 | 3.00E-21 |
| Age        | 1.028451721     | 1.015150215     | 1.041921359 | 2.38E-05 |
| UBE2C      | 1.018330727     | 1.012673308     | 1.02505585 | 1.62E-09 |

HR, hazard ratio.

[European Journal of Histochemistry 2021; 65:3196]
Identification of potential signaling pathways associated with UBE2C in RCC

Based on the differential expressed genes (DEGs) extracted from TCGA database, we explored the signaling pathways involved in development of RCC by GO and KEGG analysis. As seen in Figure 3A and Table 5, GO analysis revealed that DEGs were mostly distributed in cell division (n=86), mitotic nuclear division (n=67), and sister chromatid cohesion (n=45) process. KEGG analysis revealed significance of UBE2C in about 17 signal pathways in which cell cycle was the most important pathway (p<0.001) (Figure 3B). About 40 DEGs were enriched in cell cycle (Table 6). Then a total of 13 DEGs was enriched in DNA replication and p53 signaling pathway (Figure 3B, Table 6). It is known to us that the signaling pathways including cell cycle, cell division, p53 signaling all play important roles in tumor. So it is conceived that UBE2C might regulate one or several of these pathways in RCC.

Table 4. Multivariate COX analysis of 525 RCC patients from TCGA database.

| Term | HR (lower 0.95) | HR (upper 0.95) | p-value |
|------|----------------|----------------|---------|
| Gender | 1.052653432 | 1.49057425 | 0.7675768 |
| T | 0.861615988 | 1.26288967 | 0.445157108 |
| N | 0.893263818 | 1.052268001 | 0.176881432 |
| M | 1.08647467 | 1.76274555 | 0.736802667 |
| Stage | 2.081291149 | 3.01680225 | 0.000108772 |
| Age | 1.030989721 | 1.045486935 | 1.58E-05 |
| UBE2C | 1.01312908 | 1.020327737 | 0.00017179 |

Table 5. GO enrichment analysis of differential expression genes in RCC.

| Id | Term | Count | p-value | p adjust |
|----|------|-------|---------|-----------|
| GO:0051301 | Cell division | 86 | 6.50E-48 | 1.13E-44 |
| GO:0007067 | Mitotic nuclear division | 67 | 6.75E-40 | 1.17E-36 |
| GO:0007062 | Sister chromatid cohesion | 45 | 5.59E-37 | 9.54E-34 |
| GO:0005654 | Nucleoplasm | 212 | 3.13E-33 | 4.47E-30 |
| GO:006260 | DNA replication | 47 | 2.50E-30 | 4.34E-27 |
| GO:0007717 | Condensed chromosome kinetochore | 31 | 9.70E-23 | 1.38E-19 |
| GO:0000082 | G1/S transition of mitotic cell cycle | 33 | 2.79E-22 | 4.84E-19 |
| GO:0005515 | Protein binding | 415 | 5.73E-22 | 8.67E-19 |
| GO:0005634 | Nucleus | 292 | 2.14E-21 | 3.05E-18 |
| GO:000776 | Kinetochore | 29 | 2.41E-21 | 3.45E-18 |

Table 6. GO enrichment analysis of differential expression genes in RCC.

| ID | Term | Count | p-value | p adjust |
|----|------|-------|---------|-----------|
| hsa04110 | Cell cycle | 40 | 4.66E-28 | 9.7E-26 |
| hsa03030 | DNA replication | 13 | 1.48E-10 | 1.59E-08 |
| hsa03460 | Fanconi anemia pathway | 13 | 3.96E-08 | 2.26E-06 |
| hsa04914 | Progestosterone-mediated oocyte maturation | 17 | 7.11E-08 | 3.81E-06 |
| hsa04114 | Oocyte meiosis | 18 | 4.11E-07 | 1.51E-05 |
| hsa05166 | Human T-cell leukemia virus 1 infection | 27 | 4.24E-07 | 1.51E-05 |
| hsa04115 | p53 signaling pathway | 13 | 1.41E-06 | 4.32E-05 |
| hsa03410 | Base excision repair | 7 | 0.00001300 | 0.00003852 |
| hsa04218 | Cellular senescence | 16 | 0.00003053 | 0.00008651 |
| hsa03013 | RNA transport | 16 | 0.00008651 | 0.00002485 |
| hsa03440 | Homologous recombination | 7 | 0.00003053 | 0.00132725 |
| hsa05130 | Pathogenic Escherichia coli infection | 8 | 0.00005051 | 0.00132737 |
| hsa03050 | Proteasome | 7 | 0.00101273 | 0.00171405 |
| hsa03430 | Mismatch repair | 5 | 0.00117070 | 0.00178950 |
| hsa05203 | Viral carcinogenesis | 16 | 0.00245251 | 0.00498952 |
| hsa00240 | Pyrimidine metabolism | 10 | 0.00340741 | 0.00457415 |

[European Journal of Histochemistry 2021; 65:3196]
**UBE2C is important for cell proliferation in RCC**

To verify the real function of *UBE2C* in RCC, *UBE2C* was knocked down in 786-O cells. The knockdown efficiency of *UBE2C* in 786-O cells was over 66% (Figure 4A). Then by CCK-8 assay, we found that the growth of 786-O cells was dramatically inhibited at third day of culture. The proliferation fold in *UBE2C* knockdown group was only 1.53 but it was 3.49 in the control (Figure 4B). Therefore, *UBE2C* was essential to the growth of RCC cells.

**Figure 2.** Overall survival (OS) and progression-free survival (PFS) curves of RCC patients based on the expression of *UBE2C*. A) OS curve based on TCGA data. B) PFS curve based on TCGA data.

**Figure 3.** GO and KEGG analysis of *UBE2C*-associated pathways. A) GO analysis showed enrichment of differential expression genes. B) KEGG analysis showed the enriched signaling pathway.
**UBE2C contributes to cell migration in RCC**

Tumor cells often have potent migration ability according to the previous study. In transwell assay, we found that 786-O cells couldn’t transmit through the chamber effectively. The number of transmitted cells in UBE2C knockdown group was decreased by 44% compared to the control (Figure 4 C,D). The results suggested that UBE2C conferred migration ability to 786-O cells.

**Discussion**

UBE2C is an important gene in cancer. For example, in prostate cancer, silence of UBE2C prevents cell growth. Methylation of UBE2C lead to gene instability. Over-expression of UBE2C is closely correlated to invasion and pathological stage in ovarian cancer. In this study, UBE2C was firstly demonstrated to be clinically associated with progression and prognosis in RCC patients. This was consistent with previous studies in other cancers such as ovarian, gastric cancer.

UBE2C is also shown to be associated with poor prognosis in cancers. In this study, we demonstrated that patients with high UBE2C expression displayed short survival time and decreased PFS, suggesting that UBE2C might be a prognostic factor in RCC. This was further supported by multivariate COX analysis, which suggested UBE2C as a critical gene in RCC. Taken together, UBE2C played critical roles in development and progression of RCC and might be a new biomarker for diagnosis or prognosis in advanced RCC.

RCC is a malignant disease affected by multiple factors and a series of signaling pathways contributed to the initiation or progression of RCC. In this study, the DEGs between tumor tissues and normal tissues were extracted from the TCGA databases followed by GO enrichment analysis. As stated above, the most correlated process was cell division in which 86 DEGs were enriched. Then 67 DEGs were enriched in mitotic nuclear division and 47 DEGs in DNA replication process. The three processes are known to play important roles in embryonic development orhomeostasis. Recent studies showed that aberrant in these processes often causes severe diseases or abnormalities such as cancer. So, it is possible that UBE2C might also regulate cell division, DNA replication, and mitotic nuclear division in RCC. In KEGG analysis, 40 DEGs was enriched in cell cycle pathway while 13 DEGs in DNA replication pathway. Accelerated cell division was common in cancer and was associated with unlimited cell proliferation and accelerated cell cycle. DNA replication was also an active process in cancer. Here, KEGG analysis showed that cell cycle and DNA replication were two top pathways in RCC. Indeed, active DNA replication process provides basis for cell cycle transition. This will further contribute to the division and proliferation of cancer cells. As a result, we...
deduce that UBE2C might regulate cell cycle and DNA replication pathway in RCC.

The bioinformatics analysis showed that UBE2C played important roles in clinic in RCC. This was further supported by in vitro assay in 786-O cells. As stated in the above, knockdown of UBE2C by RNAi significantly inhibited cell proliferation and migration in 786-O cells. It is known that potent proliferation and migration ability are two common traits in cancer.\textsuperscript{26,27} So, the preliminary data in 786-O cells further confirmed the role of UBE2C in RCC. However, more experiments are needed to support the oncogenic role of UBE2C in RCC and the mechanism that how UBE2C promotes progression in RCC. In future, we plan to further detect the role of UBE2C in more than two strain cell lines in RCC, especially the effects on cell apoptosis, cell cycle, and cell invasiveness. In addition, the in vitro role of UBE2C in RCC is a very important proof to support this study.

In summary, this study proves the clinical role of UBE2C and suggests it to be an important prognostic factor in RCC. UBE2C contributes to the proliferation and migration in RCC.

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