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Inhibition of Cyclin F Promotes Cellular Senescence through Cyclin-dependent Kinase 1-mediated Cell Cycle Regulation*

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[Abstract] Objective: Kidney renal clear cell carcinoma (KIRC) is a common renal malignancy that has a poor prognosis. As a member of the F box family, cyclin F (CCNF) plays an important regulatory role in normal tissues and tumors. However, the underlying mechanism by which CCNF promotes KIRC proliferation still remains unclear. **Methods:** Bioinformatics methods were used to analyze The Cancer Genome Atlas (TCGA) database to obtain gene expression and clinical prognosis data. The CCK8 assay, EdU assay, and xenograft assay were used to detect cell proliferation. The cell senescence and potential mechanism were assessed by SA-β-gal staining, Western blotting, as well as ELISA. **Results:** Our data showed that CCNF was highly expressed in KIRC patients. Meanwhile, downregulation of CCNF inhibited cell proliferation *in vivo* and *in vitro*. Further studies showed that the reduction of CCNF promoted cell senescence by decreasing cyclin-dependent kinase 1 (CDK1), increasing the proinflammatory factors interleukin (IL)-6 and IL-8, and then enhancing the expression of p21 and p53. **Conclusion:** We propose that the high expression of CCNF in KIRC may play a key role in tumorigenesis by regulating cell senescence. Therefore, CCNF shows promise as a new biomarker to predict the clinical prognosis of KIRC patients and as an effective therapeutic target.
Key words: cyclin F; kidney renal clear cell carcinoma; clinical outcome; cyclin-dependent kinase 1; senescence

Renal cell carcinoma (RCC) is the most common malignant tumor derived from the kidney. There are approximately 210 000 new cases diagnosed worldwide each year, accounting for 2%–3% of all cancers[1]. As the main histological subtype of RCC, kidney renal clear cell carcinoma (KIRC) now accounts for 80%–90% of RCC patients[2]. Even if efforts are taken by researchers to facilitate an early diagnosis and to ensure a multi-disciplinary therapeutic approach for KIRC, the clinical prognosis and efficacy are still not ideal due to its malignant biological characteristics[3]. KIRC has triggered huge affliction to the families of patients and is a weighty medical burden to society[4]. The possible cause of this adverse situation might be the lack of reliable and effective molecular markers for early diagnosis and targeted therapy of KIRC patients. Therefore, further studies are required to explain the underlying pathogenesis of KIRC as well as to explore novel useful biomarkers for diagnosis, prognosis, and treatment.

According to the Gene Nomenclature Committee of the Human Genome Organization, the cyclin gene group consists of 31 members. By forming the Skp1-Cul1-F-box protein ubiquitin ligase complex, cyclin F (CCNF) is implicated in controlling centrosome duplication and preventing genome instability[5]. During the cell cycle, the CCNF protein level fluctuates, increasing and reaching the peak in the G2 phase[6]. CCNF takes part in multiple biological processes, including cell cycle transition, DNA damage repair[7], and chromatin homeostasis[5]. The abnormal expression of CCNF is related to several neurological diseases and various forms of cancer[8]. Several cancers, such as liver hepatocellular carcinoma and invasive breast carcinoma, have an elevated expression level of CCNF[9, 10]. CCNF is associated with tumorigenesis, chemo-resistance, and poor clinical outcomes[6, 7].

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However, the potential role and specific mechanism of CCNF in KIRC are not fully clear.

In this study, we used various bioinformatics analysis methods to determine the CCNF expression and interpreted the significance of abnormal CCNF expression in KIRC and its potential value for prognosis and diagnosis by analyzing the RNA sequencing and clinical data of KIRC patients retrieved from The Cancer Genome Atlas (TCGA) database. In addition, the CCNF-related functions and pathways were investigated by tumor proliferation and colony formation assays *in vitro* and observation of tumorigenesis *in vivo*. Moreover, the role of CCNF on cell senescence and the cyclin-dependent kinase 1 (CDK1)/P53 pathway to promote tumor progression was determined.

1 MATERIALS AND METHODS

1.1 Data Processing

Data were acquired from the TCGA KIRC database. We analyzed TCGA RNA-seq data and normalized them according to fragments per kilobase of exon per million. Data from 611 KIRC patients were acquired and processed with the methods described by Xia *et al*[11].

1.2 Functional Annotation of CCNF-Associated Differentially Expressed Genes (DEGs) in KIRC Tumors

With the application of the "clusterProfiler" R-package, we used Gene Set Enrichment Analysis (GSEA) to process and analyze our gene enrichment dataset[12, 13]. Hallmark MSigDB gene sets were analyzed as reference gene sets. For protein-protein interaction networks, STRING was used for the interaction prediction[14].

1.3 Clinicopathological Characteristics of KIRC Patients Associated with CCNF

According to the CCNF mRNA expression levels, we divided the patients into high-CCNF-expression and low-CCNF-expression groups. For clinicopathological analysis and comparison, we applied the Wilcoxon rank sum test or Pearson's chi-squared test. To reveal the relationship between the analyzed clinicopathological characteristics and CCNF expression, logistic analysis was applied.

1.4 Clinical Significance of CCNF Expression on KIRC Patient Survival

To investigate the significance of CCNF expression, we acquired the clinical outcomes of KIRC patients from an open resource, which was published by a KIRC clinical research institute, including overall survival, progression-free interval, and disease-specific survival. To determine data accuracy, receiver operating characteristic (ROC) curve analysis was applied[15].

1.5 Cell Lines and Antibodies

Kidney renal clear cell 786-O and KTCTL-140 cell lines were obtained from Nanjing Cobioer Co., Ltd. (China). 786-O, KTCTL-140, and HEK293T were cultured in Dulbecco's modified Eagle medium containing 10% fetal bovine serum, 1% penicillin, and 1% streptomycin. The following antibodies were used: CCNF (Affinity, US, Cat. No. DF4238), CDK1 (Cell Signaling Technology, US, Cat. No. 4370), P21 (Cell Signaling Technology, US, Cat. No. 2947), P53 (Cell Signaling Technology, US, Cat. No. 9282), and β-actin (Cell Signaling Technology, US, Cat. No. 58169).

1.6 Western Blotting

The cells were cultured, lysed with NP-40 (30 min, 4°C), and centrifuged (12 000 *g*×10 min). The supernatant was collected, and the protein concentration was determined with a BCA assay kit (Thermo, US, #23227). The target proteins were separated by SDS-PAGE and then transferred onto PVDF membranes (EMD Millipore, Germany, Cat. No. ISEQ00010). The membranes were incubated with primary antibodies overnight at 4°C, washed with TBS-T three times, then incubated with the corresponding IRDye® 800CW Goat anti-Rabbit IgG (H+L) (1:20 000; LI-COR, US, Cat. No. 926-32211) at room temperature for 1 h, washed three times with TBS-T, and finally imaged.

1.7 shRNA and Transfection

The sequences 5′-CCGGCACAGAGCAATGCTATGGAATCTCGAGATTCCATAGCATTGCTCTTGTTTTTTG-3′ and 5′-CTCAACTCTCAACTCAC-TGTA-3′ were used for plasmid construction for CCNF knockdown. After construction, we transfected 293T cells for 48 h. Next, the supernatant was collected and then the indicated cell lines were infected for 48 h. Puromycin (Sigma-Aldrich, Germany) was used to select the stably transfected cells for 2 days.

1.8 Colony Formation Assay

For colony formation, the indicated cell lines were seeded in 12-well plates for 2 weeks. Each well contained 800 cells. After 2 weeks, the cells were fixed with 4% paraformaldehyde for 1 h and stained by crystal violet for 30 min. For colony quantification, ImageJ software was used.

1.9 Mouse Tumor Xenograft Model

This study was approved by the Huazhong University of Science and Technology Ethics Committee. All mouse experiments were approved by the Animal Care and Use Committee of Tongji Hospital. Four-week-old male nude mice were obtained from GemPharmatech (China). The mice were divided randomly into the indicated groups. For xenograft setup, the mice were injected with 1×10^6 780-O cells subcutaneously, and the tumor was harvested after 28 days.

1.10 ELISA and SA-β-gal Assay

The interleukin (IL)-6 and IL-8 levels secreted

by the indicated cells were tested by the respective ELISA kit, separately (Abclonal Technology, China, #RK00023). The SA-β-gal assay was performed by a cellular senescence kit (Beyotime, China, C0602), according to the manufacturer's procedures.

1.11 Statistical Analysis

Statistical analysis was performed by Prism V.8.0. Unless otherwise indicated, the data are represented as the mean ± SD. If *P*-value <0.05, data were denoted as statistically significant.

2 RESULTS

2.1 Gene-Expression Profiling of CCNF in Different Cancers and Related DEGs in KIRC

By analyzing the mRNA expression levels of CCNF in different cancers from TCGA database, we found that CCNF was significantly overexpressed in 17 of 33 types of cancer, especially those located in the intracranial and urogenital tract (fig. 1A). Compared to precancerous tissues, CCNF showed a prevalent upregulation in KIRC tumors (P<0.001, fig. 1B). Interestingly, the mRNA expression level of CCNF did not appear to be significantly decreased among those tumors. Next, we decided to study the role of CCNF-mediated DEGs among KIRC patients by GSEA. Our results showed that the CCNF-associated DEGs were enriched in clusters associated with cell proliferation and senescence (fig. 1C and 1D), such as cyclin events during the G2M transition [normalized enrichment score (NES)=1.777, adjusted P=0.013, false discovery rate (FDR)=0.010] and the cell senescence-related E2F pathway (NES=1.88, adjusted P=0.013, FDR=0.010) (fig. 1C and 1D). Thus, our GSEA results suggest that higher mRNA levels of CCNF may trigger tumorigeneses and tumor progression.

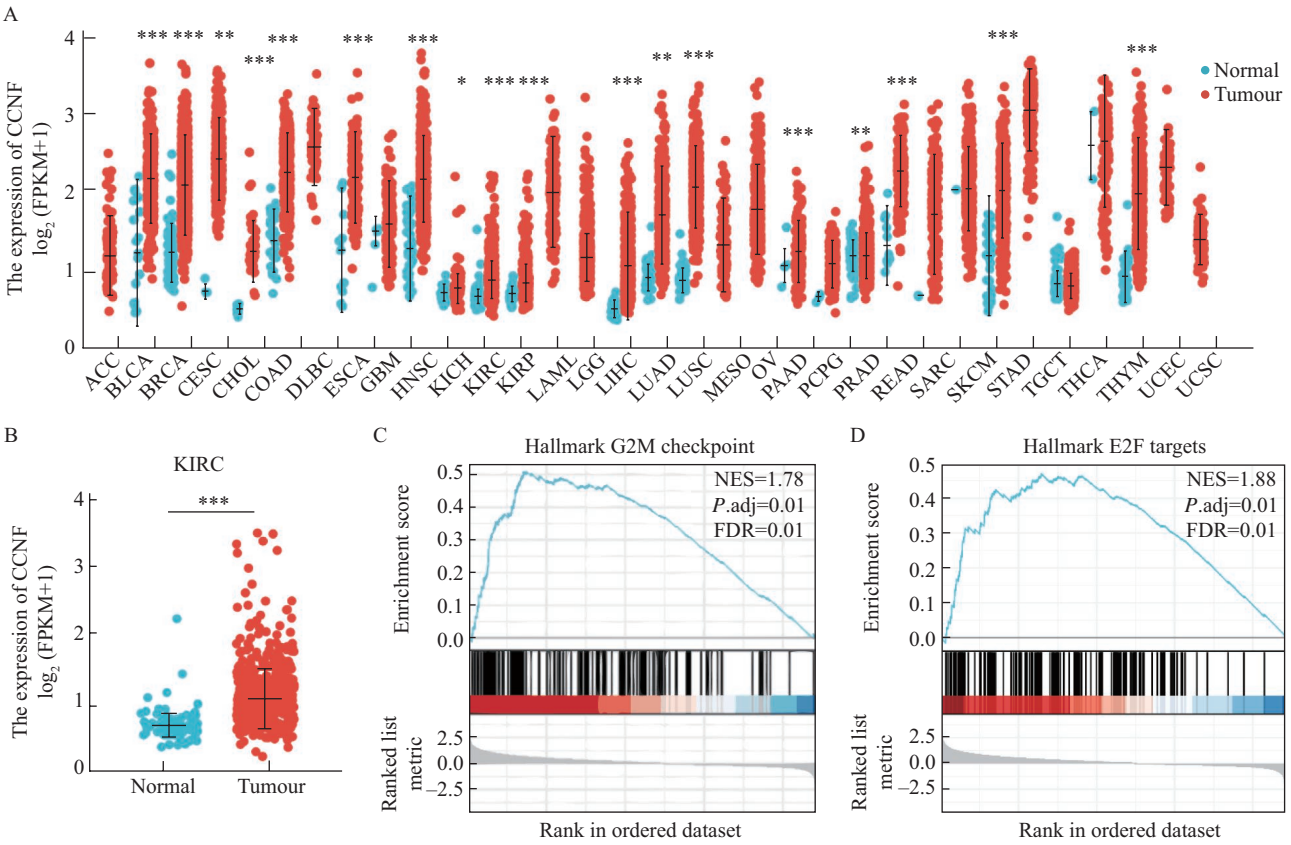

Fig. 1 Differential mRNA expression profiles in kidney renal clear cell carcinoma (KIRC) patients stratified by cyclin F (CCNF) levels
A: the comparison of CCNF expression between tumor and pericarcinoma tissue in different types of cancer based on The Cancer Genome Atlas (TCGA) database. B: The expression of CCNF was higher in KIRC than in pericarcinomas tissue. Based on the median CCNF level, 288 KIRC patients from TCGA-KIRC were stratified into high- and low-CCNF-expression groups. C and D: Gene Set Enrichment Analysis indicates that CCNF-associated differentially expressed genes were enriched in the cell cycle and cell senescence. $^{**}P$<0.01, $^{***}P$<0.001

2.2 CCNF Knockdown Inhibits KIRC Proliferation *In Vitro*

To further explore the function of CCNF during KIRC tumorigeneses, we constructed stable CCNF-knockdown cell lines in KIRC cell lines, including 786-O and KTCTL-140. Western blotting analysis was applied to verify the knockdown efficacy (fig. 2A). To investigate the relationship between the CCNF expression level and KIRC proliferation, CCK8 and EDU assays were performed. The CCK8 assay results showed that CCNF inhibition reduced KIRC cell proliferation, and the EDU assay exhibited a

consistent result (fig. 2B–2E). The colony formation assay demonstrated that CCNF silencing decreased the formation capacity of KIRC, indicating that CCNF may promote KIRC proliferation (fig. 2F and 2G). Together, our data show that CCNF promotes KIRC proliferation *in vitro*.

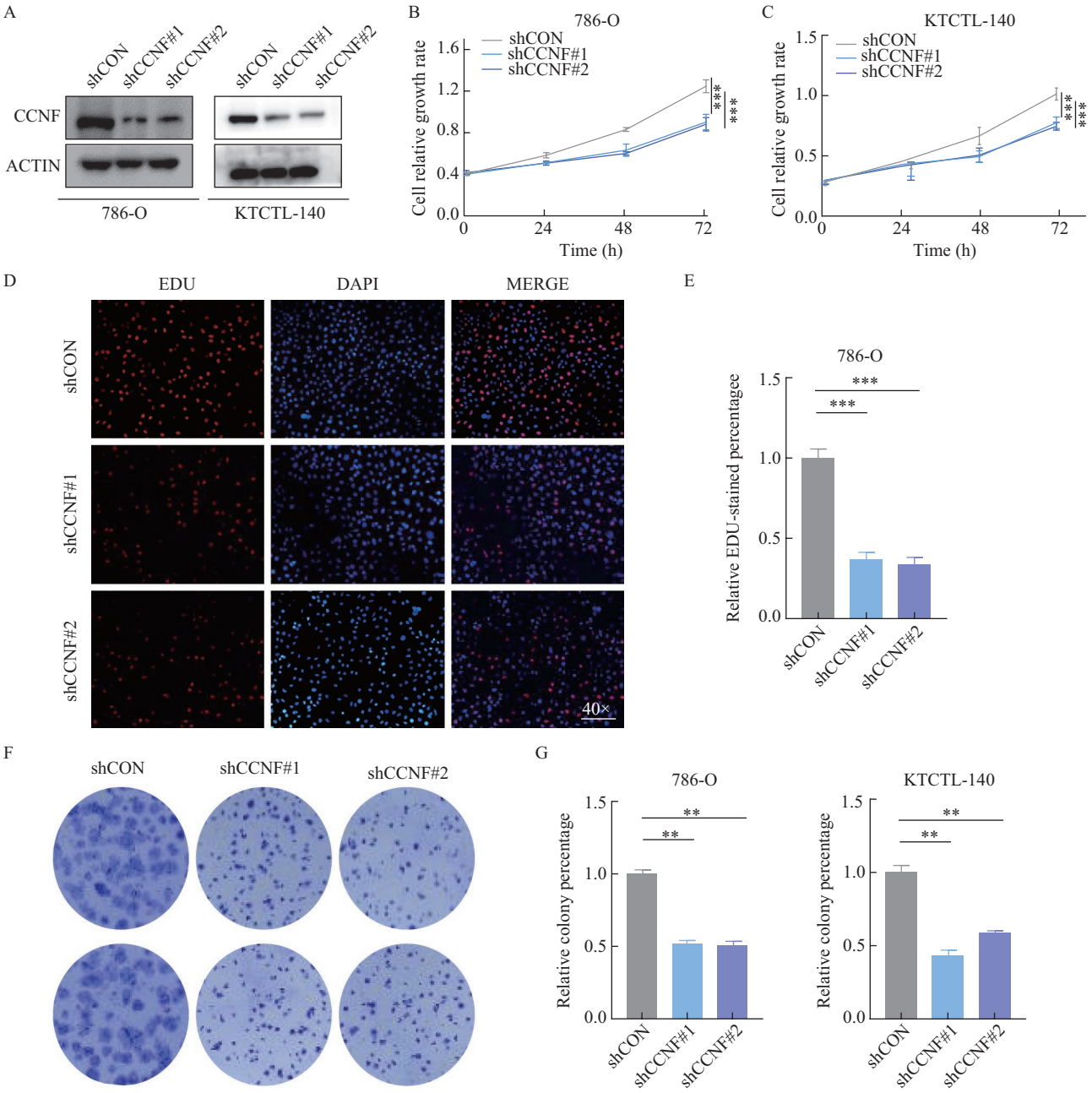

Fig. 2 Knockdown of cyclin F (CCNF) inhibits 786-O and KTCTL-140 cell proliferation and colony formation
A: 786-O and KTCTL-140 cells were transduced with lentiviruses carrying the indicated shRNA, and the protein expression was analyzed by Western blotting using the indicated antibodies. B–D: CCK8 and EDU assays were used to assess the DNA synthesis rate of the shCON, shCCNF#1, and shCCNF#2 groups. E: the percentage of EDU-positive cells in the shCON, shCCNF#1, and shCCNF#2 groups. F: Colony formation assay showed the colony formation capacity of the shCON, shCCNF#1, and shCCNF#2 groups. G: The colony number of each group was counted. Shown are the relative colony number in the shCCNF#1 and shCCNF#2 groups compared to the shCON group. $^{**}P<0.01$, $^{***}P<0.001$

2.3 CCNF Knockdown Inhibits KIRC Proliferation *In Vivo*

Since our results indicated that CCNF promoted KIRC proliferation *in vitro*, we further investigated the role of CCNF during KIRC tumorigenesis *in vivo*. By setting up a xenograft model with 786-O cells, we recorded the subcutaneous tumor size and found that CCNF inhibition reduced the KIRC tumor growth rate (fig. 3A). After 28 days, the mice in each group were sacrificed, and the xenograft tumors were gathered and weighed (fig. 3B and 3C). Since the CCNF-silenced group showed smaller tumors and a lighter weight, we further explored the proliferation rate of tumors by Ki-67 staining. Consistently, CCNF inhibition decreased

KIRC proliferation, as indicated by the Ki-67-stained percentage (fig. 3D and 3E). In short, our data suggest that CCNF knockdown inhibits KIRC proliferation *in vivo*.

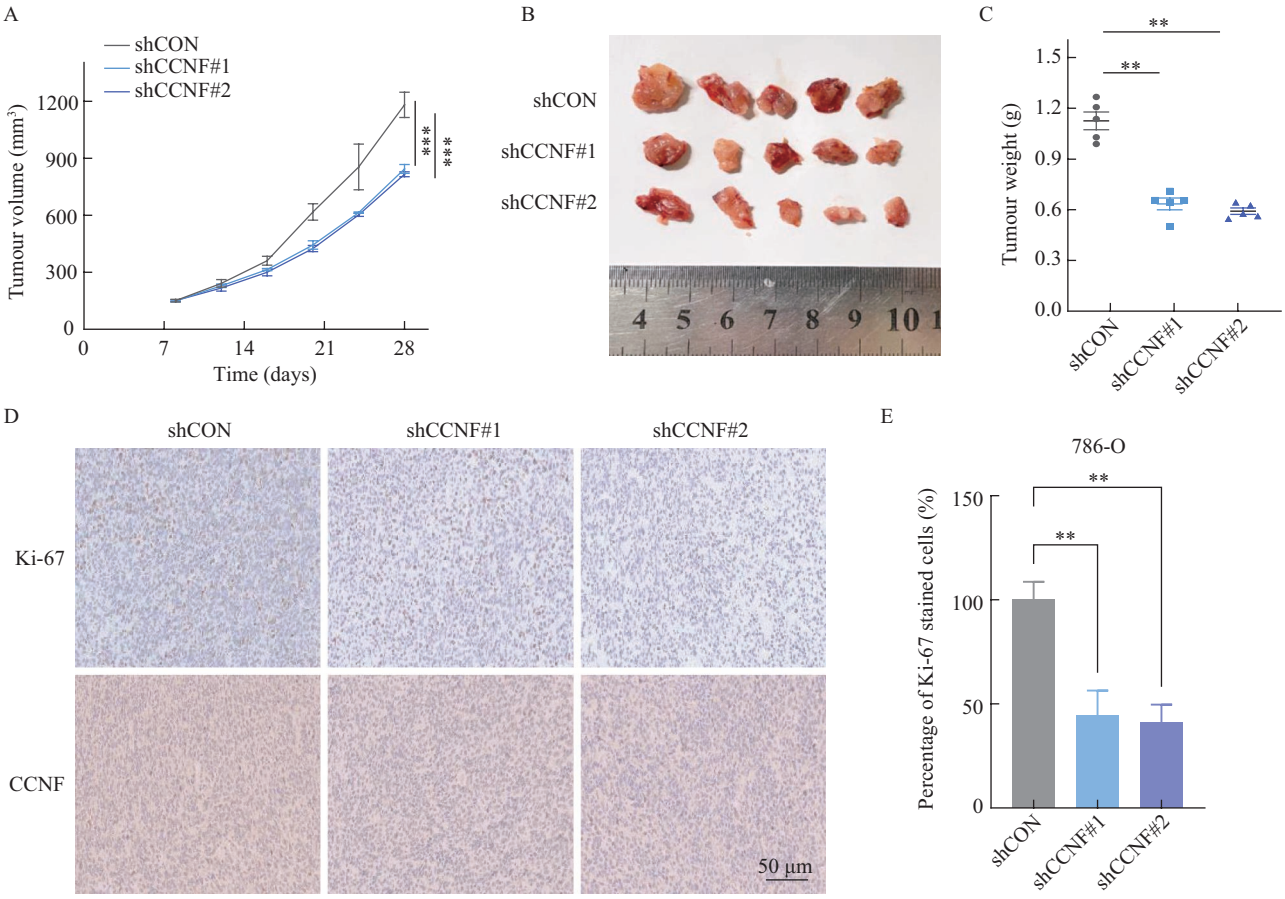

Fig. 3 Knockdown of cyclin F (CCNF) inhibits KIRC growth

A: the growth curve of mouse xenograft tumors formed by shCON, shCCNF#1, and shCCNF#2 cells (n=5). B: mouse xenografts formed by 786-O, with or without CCNF intervention. C: tumor weights after sacrificing the mice (n=5). D and E: immunohistochemical staining of xenografts using antibodies against Ki-67 and CCNF. $^{**}P$<0.01, $^{***}P$<0.001

2.4 Knockdown of CCNF Increases Cell Senescence in KIRC

Our data showed that CCNF promoted KIRC both *in vitro* and *in vivo*. Next, we further explored the mechanism under this phenotype. With the application of protein interaction prediction by STRING, we found that CCNF was associated with several cell-cycle regulator proteins, which is consistent with our previous GSEA results (fig. 4A). Given the vital role of CDK1 in cell senescence reported in mammals, we then wondered whether CCNF plays a regulatory role in cell senescence in KIRC. Western blotting assays showed that CCNF inhibition downregulated CDK1 and upregulated p53 and p21 (fig. 4B). Since p53 and p21 are considered downstream of CDK1 and are biomarkers for cell senescence, we further investigated the levels of cell senescence-associated cytokines, including IL-6 and IL-8, with the inhibition of CCNF. Our data showed that the secretion of cell senescence-associated cytokines IL-6 and IL-8 was significantly upregulated (fig. 4C–4F). We further performed an SA-β-gal assay to confirm that CCNF promotes KIRC proliferation by inhibiting cell senescence. Representative images and quantitative analyses revealed increased numbers of senescent cells in the shCCNF groups (fig. 4G and 4I). Therefore, our data reveal that CCNF plays a critical role in inhibiting KIRC cell senescence and that targeting CCNF may be a novel therapeutic strategy for KIRC patients.

2.5 Relationship between CCNF Expression and Clinicopathological Characteristics in KIRC Patients

By analyzing CCNF expression in patients with different clinicopathological characteristics, we found that CCNF expression was significantly increased in the T stage, especially during T3 and T4 (fig. 5A), M stage M1, N stage N1 (fig. 5B and 5C), clinical stage Ⅲ and Ⅳ (fig. 5D), and histological stage G3 and G4 (fig. 5E). However, CCNF expression was significantly reduced in patients with low serum calcium levels (fig. 5F). These results indicate that CCNF expression is highly associated with the KIRC clinicopathological grade.

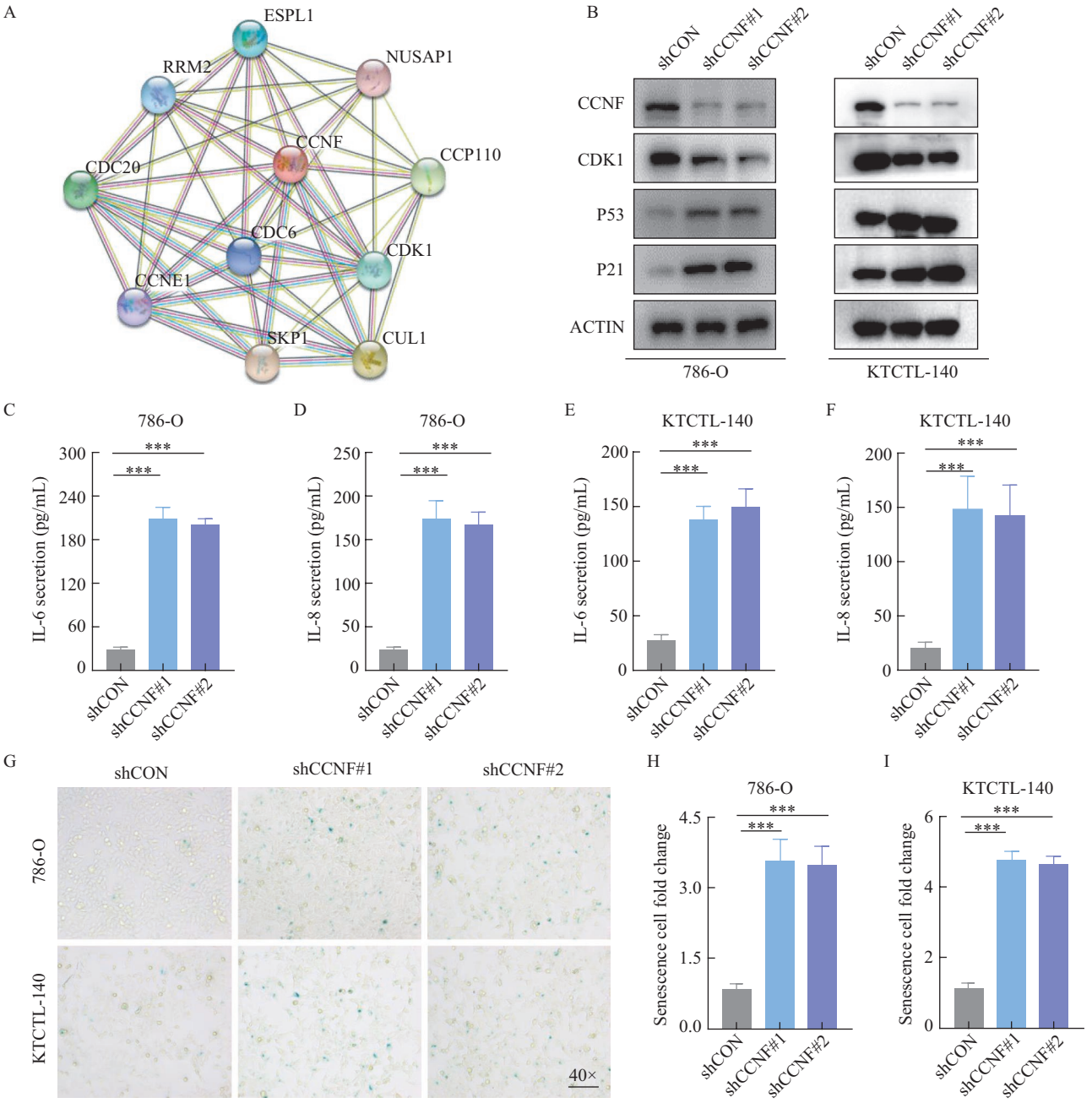

Fig. 4 Knockdown of cyclin F (CCNF) induces KIRC cell senescence

A: protein-protein interaction network of the top 10 interacting genes related to CCNF. B: 786-O cells were transduced with shCCNF lentiviruses, and the protein expression was analyzed by Western blotting using the indicated antibodies. C–F: The levels of interleukin (IL)-6 and IL-8 secreted by 786-O and KTCTL-140 cells after transfection with shCCNF, respectively. G: SA-β-gal staining analysis in 786-O and KTCTL-140 cells transfected with shCCNF, respectively. H, I: The relative fold change of the SA-β-gal staining ratio in each shCCNF group was calculated and compared to that of the shCON group. $^{***}P<0.001$

2.6 The Predictive Value of CCNF in the Diagnosis and Prognosis of KIRC Patients

We further investigated the clinical value of CCNF during diagnostic differentiation by ROC curves. With an area under the curve of 0.871, CCNF showed a high sensitivity and specificity for the diagnosis of KIRC (fig. 6A). The Kaplan-Meier analysis further validated the prediction of clinical outcomes by CCNF, including the overall survival [hazard ratio (HR): 1.89, $P<0.001$], the disease-specific survival (HR: 2.51, $P<0.001$), and the progression-free interval (HR: 1.96, $P<0.001$). The high-CCNF-expression group had statistically worse characteristics than the low-CCNF-expression group (fig. 6B–6D).

3 DISCUSSION

In this study, we identified that the inhibition of CCNF suppressed KIRC proliferation both *in vitro* and *in vivo*. Mechanistically, we found that CCNF promoted KIRC proliferation by inhibiting cell senescence through the CDK1-P53 signaling pathway.

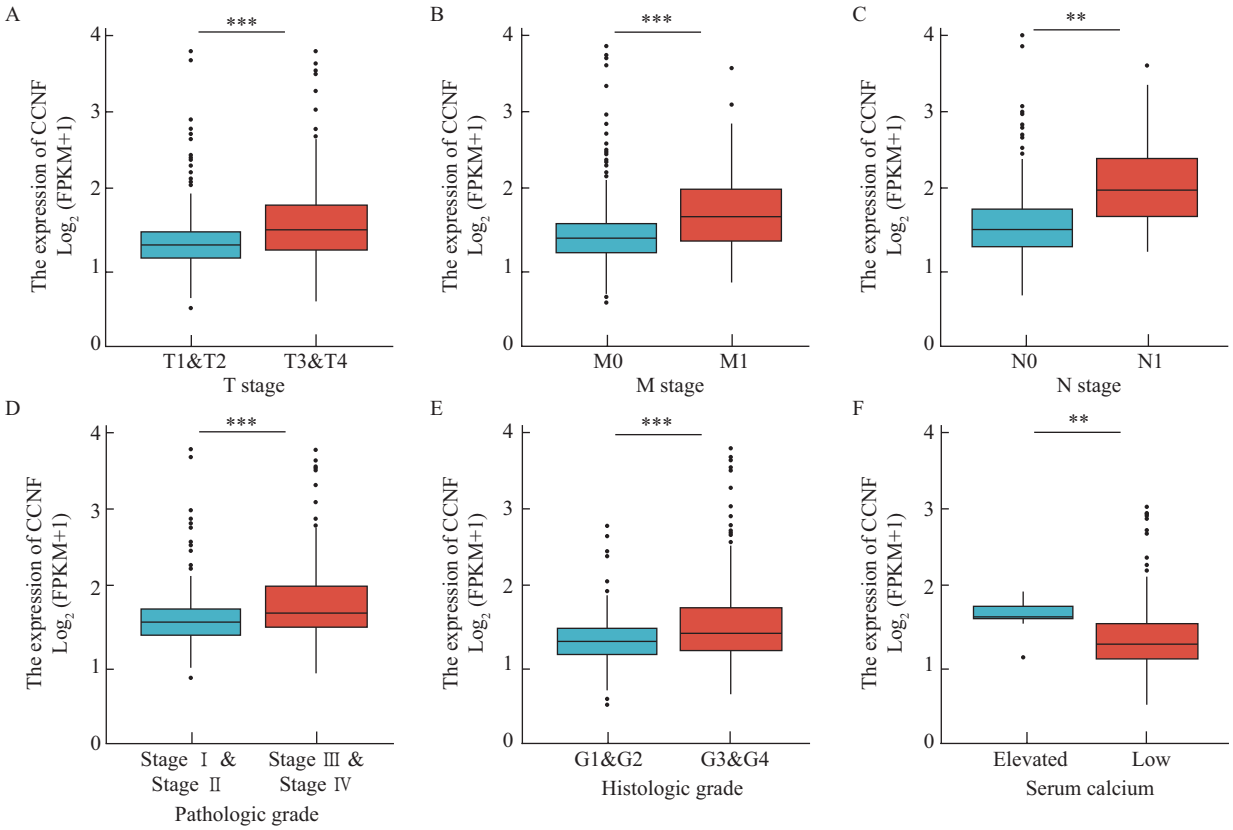

Fig. 5 Cyclin F (CCNF) expression is associated with clinicopathological characteristics in kidney renal clear cell carcinoma (KIRC) patients

A–F: The Wilcoxon rank sum test was applied to analyze the association of CCNF expression with the clinical T stage, clinical N stage, clinical M stage, pathologic status, histologic grade, and serum calcium level. $^{**}P<0.01$, $^{***}P<0.001$

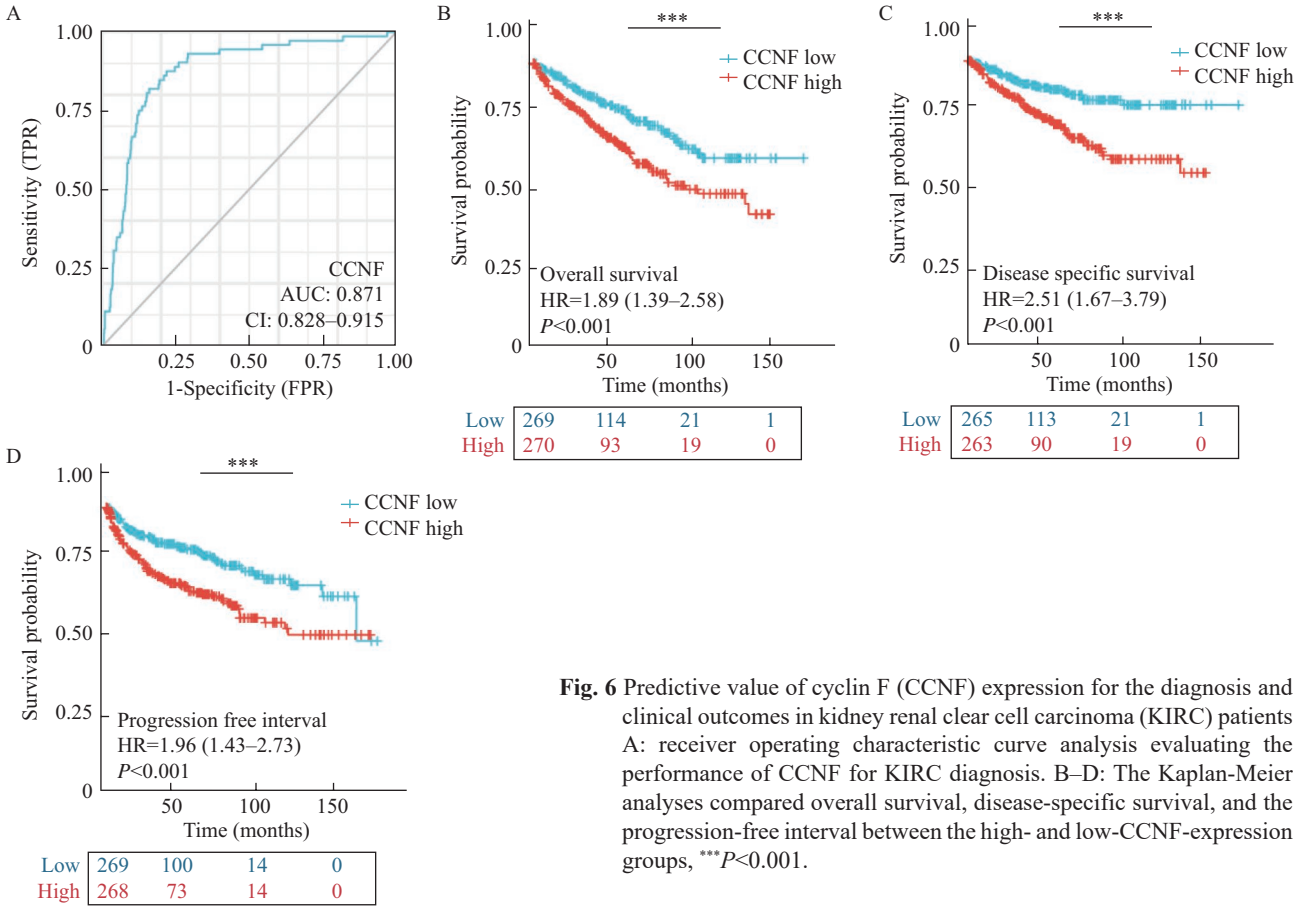

Fig. 6 Predictive value of cyclin F (CCNF) expression for the diagnosis and clinical outcomes in kidney renal clear cell carcinoma (KIRC) patients

A: receiver operating characteristic curve analysis evaluating the performance of CCNF for KIRC diagnosis. B–D: The Kaplan-Meier analyses compared overall survival, disease-specific survival, and the progression-free interval between the high- and low-CCNF-expression groups, $^{***}P<0.001$.

Our data demonstrate that CCNF might be used as a biomarker or a prognostic predictor in KIRC patients and could be a potential treatment target for KIRC.

CCNF has been reported to be upregulated among various types of cancer[8]. Consistently, by accessing the TCGA database, we found that CCNF is overexpressed in most cancers, including KIRC. Interestingly, among the 33 types of tumors analyzed, none of them showed a decreased mRNA level of CCNF. In addition, most of the cell cycle and cell senescence-associated mRNA levels were downregulated and identified as DEGs, while CCNF was upregulated, thus indicating that CCNF might play a vital role during cell cycle transition and cell senescence.

As a founding member of the F box family, CCNF was first characterized by the presence of an F-box motif[16]. Further CCNF-related discoveries have been established in multiple tumors. Li *et al* have reported that CCNF promotes ovarian cancer tumorigenicity *in vitro*[17]. It also has been reported that CCNF deficiency results in severe mitotic defects, multipolar spindles, and supernumerary centrosomes, which increase the ovarian cancer apoptotic rate[18]. The above abnormal phenotypes are seen consistently in different cancer models, indicating that CCNF has a general correlation with human cancer. In our study, we found that CCNF was significantly elevated in several urogenital cancers, including KIRC, chromophobe renal carcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, and endocervical adenocarcinoma. Consistent with previous studies, our data showed that CCNF promoted KIRC proliferation both *in vivo* and *in vitro*. Mechanistically, our results indicate that CCNF might promote KIRC proliferation by inhibiting cell senescence through the CDK1-p53 signaling pathway.

As a cell cycle regulator, CDK1 exhibits various biological functions, such as cell cycle regulation, DNA damage repair, cell apoptosis, and so on[19]. A recent study also has proven the crucial role of CDK1 during chemoresistance[20]. In addition, by studying single cells, it has been reported that residual CDK1/2 activity after DNA damage promotes senescence[21]. In our study, we found that CCNF silencing downregulated CDK1 expression and upregulated both p21 and p53. Given the crucial role of p21 and p53 in promoting senescence[22], we assumed that reducing the amount of CCNF might promote KIRC senescence by increasing the p53 and p21 levels. This speculation was validated by our SA-β-gal assay, which indicated that the downregulation of CCNF might occur through mediating CDK1-activated senescence pathways to inhibit the proliferation of KIRC.

In conclusion, the present study demonstrated that CCNF expression is highly elevated in KIRK. KIRC patients with high-CCNF expression showed a lower overall survival than those with low-CCNF expression. Therefore, a high-expression level of CCNF seems to be a potential specific prognostic biomarker for a worse prognosis in individuals with KIRC. Moreover, our data indicate that CCNF promotes KIRC cell proliferation through the CDK1-p53/p21 cell senescence pathway. Furthermore, we have shown that CCNF may act as a potential prognostic marker and a therapeutic target for KIRC.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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