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Knockdown of kinesin family member 2C restricts cell proliferation and induces cell cycle arrest in gastric cancer

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Summary. Kinesin family member 2C (KIF2C) was reported to act as a vital player in several human cancers. However, the exact function of KIF2C in gastric cancer (GC) is poorly understood. In the present study, the potential role of KIF2C was studied in gastric cancer by bioinformatics analysis and proliferation assay. KIF2C expression was detected using reverse transcription-quantitative polymerase chain reaction and western blot. Our data showed that the expression of KIF2C was increased in different tumor tissues, including GC. KIF2C was overexpressed in GC tissues and might be used as a diagnostic and prognostic biomarker for GC. KIF2C expression was correlated with immune infiltration and the levels of cell cycle-related genes in GC. Moreover, silencing of KIF2C can cause cell cycle arrest, and inhibit the proliferative ability of GC cells. Thus, our studies revealed that KIF2C levels might serve as a promising biomarker for diagnosis and prediction of prognosis of GC, and targeting KIF2C might be an effective therapeutic strategy for GC.

Key words: Kinesin family member 2C, Gastric cancer, Cell cycle arrest, Immune infiltration

Introduction

Gastric cancer (GC) is burgeoning throughout the world, and is the fifth most common neoplasm and the third leading cause of cancer mortality (Bray et al., 2018). GC has become a huge medical burden throughout the world, with a high cost of treatment (Thrift and El-Serag, 2020). Curative surgery is considered the only way to treat GC (Van Cutsem et al., 2016). However, because of a lack of the early symptoms, many patients are diagnosed at the advanced stage and cannot be operated (Johnston and Beckman, 2019). Hence, early diagnosis is critical for improving the outcome of GC patients and prolonging their survival time. Thus, seeking an effective diagnostic biomarker is of major importance for GC treatment.

Kinesin family member 2C (KIF2C), also called mitotic centromere-associated kinesin, belongs to the kinesin-13 family and acts as a pivotal microtubule modulator (Ritter et al., 2015a). KIF2C is composed of a conserved kinesin motor domain and is capable of depolymerizing microtubules by inducing the removal of tubulin subunits from the microtubule polymer end (Ritter et al., 2015b). Several studies showed that KIF2C acts as a vital player during mitosis (McHugh et al., 2019). It was found that the upregulation of KIF2C induced the instability of chromosomes, thereby increasing the chances of tumorigenesis (Wagenbach et al., 2020). Furthermore, KIF2C is considered as a crucial regulator of cytoskeletal remodeling during tumorigenesis. KIF2C is reported to be overexpressed in various human cancers, such as lung adenocarcinoma, hepatocellular carcinoma, and acute lymphoblastic leukemia (Bai et al., 2019; Li et al., 2020; Oh et al., 2020). Its over-expression may act as an independent biomarker for the prognosis of glioma (Bie et al., 2012). Its upregulation in breast tumor is associated with a poor prognosis for patients. This demonstrates the diagnostic and prognostic role of KIF2C in breast cancer (Song et al., 2018). However, the function of KIF2C and its underlying mechanism in GC progression are still not well investigated.

In this study, we assess the potential role of KIF2C as a prognostic biomarker for GC and analyze the relationship between KIF2C and cell cycle progression in GC. We found that the expression of KIF2C in GC patients may be used as a prognostic marker. The silencing of KIF2C restricts cell proliferation and halts

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cell cycle progression in GC, thereby making it a promising therapeutic target for GC.

Materials and methods

Patient samples

All the experimental procedures were permitted by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital. GC samples and their corresponding normal samples were excised from 35 patients that received surgery in the Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, and the specimens were confirmed by pathological examination. Informed consent was signed before the patient received surgery.

Cell culture

Human normal gastric mucosa cells (GES-1) were acquired from Sunncell (Wuhan, China) and cultured in Dulbecco's Modified Eagle's medium plus 10% fetal bovine serum (FBS; Procell, Wuhan, China) and 1% penicillin/streptomycin (Solarbio, Beijing, China) in 5% CO_2/95% air at 37°C. Human GC cells (AGS, MKN-45, NCI-N87, and SNU-1) were acquired from Procell (Wuhan, China). AGS were grown in Ham's F-12 medium containing 10% FBS and 1% penicillin/streptomycin under 5% CO_2/95% air at 37°C. MKN-45, NCI-N87, and SNU-1 cells were cultured in RPMI-1640 medium plus 10% FBS and 1% penicillin/streptomycin under 5% CO_2/95% air at 37°C.

Western blotting

Total protein was isolated from GC tissues and cells using the lysis buffer (Beyotime, Shanghai, China) containing protease inhibitors and NP-40. A Pierce Bicinchoninic Acid Protein Assay kit (Thermo Fisher Scientific, San Jose, CA, USA) was applied for the quantification of extracted proteins. The protein samples (20 μg) were then subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis, followed by electrotransfer to a polyvinylidene fluoride membrane (Merck Millipore, Darmstadt, Germany). Subsequently, the membrane was sealed in 5% fat-free milk for 1h at 25°C, followed by incubation overnight at 4°C with the anti-KIF2C (1: 1000 dilution; Novus Biologicals, Littleton, CO, USA) or anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH; 1:1000 dilution; Novus Biologicals) antibody. After rinsing with phosphate buffer saline (PBS), these cells were immunoblotted for 1h with the goat anti-mouse IgG secondary antibody (1:2000 dilution; Novus Biologicals) at 25°C. Membranes were incubated with enhanced chemiluminescence reagent (Beyotime, Shanghai, China) and blots were photographed with a chemiluminescence imaging system (Liuyi Biotechnology, Beijing, China).

Cell cycle assay

GC cells were seeded in 6-well plates. After treatment, cells were collected, centrifuged, and suspended in PBS. After fixation with 75% alcohol for 1h, the cells were stained with viability staining solution (5 μg/mL propidium iodide, 20 μg/mL RNase in PBS) for 30 min at 25°C in the dark, and flow cytometry (BD Biosciences, San Diego, CA, USA) was applied to analyze the cell cycle distribution.

Cell proliferation assay

Cell proliferation was assessed using the Click-iT® EdU Alexa Fluor® 488 Imaging Kit (Thermo Fisher Scientific), following the manufacturer's recommendations. Cells were collected, treated with a reaction cocktail for 30 min and then rinsed with 3% bovine serum albumin and PBS subsequently for 2 min each. Cells were dyed for 2 min with 4',6-diamidino-2-phenylindole (Solarbio) solution before washing in PBS for 2 min.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

RNA extraction was done using a total RNA extraction kit (Vazyme, Jiangsu, China). The reverse transcription was performed to obtain cDNA using ABScript RT Master Mix (Takara, Shiga, Japan), following the manufacturer's recommendations. KIF2C expression was tested using SYBR® Premix Ex Taq from Takara. The sequences of primers (GenScript, Nanjing, China) used in this work are listed as follows: GAPDH forward: 5'-AGATCCCTCCAAAATCAAG TGG-3', and GAPDH reverse: 5'-GGCAGAGATGATG ACCCTTTT-3'; KIF2C forward: 5'-TCCAGGCAATTT ATCCAAGG-3', and KIF2C reverse: 5'-CCAGTCTGG TCCTTGCTGTA-3'. The relative expression of KIF2C was computed using the $2^{-\Delta\Delta Ct}$ method. GAPDH was used as a housekeeping gene.

Bioinformatic analysis

Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/index.html) was used for the analysis of the expression profile of KIF2C in multiple tumors, and to obtain KIF2C-related genes. Metascape database (http://metascape.org/) was used to predict the function of KIF2C-related genes. The diagnostic value of KIF2C in GC was assessed using received operating characteristic (ROC) curve. Kaplan Meier plotter (http://kmplot.com/analysis/) was applied to assess the relation between KIF2C expression and Overall (OS) survival, disease-free survival (DFS), and progress-free interval (PFI) in GC patients. The association between KIF2C expression and the infiltrating levels of immune cells was analyzed

using Tumor Immune Estimation Resource (TIMER) database (https://cistrome. shinyapps.io/timer/). Cox regression analysis was applied to analyze the correlation between KIF2C expression and clinical parameters.

Statistical analysis

The data was expressed as the mean and standard deviation and analyzed using Graph Pad Prism 8 (Graphpad Software, La Jolla, CA, USA). The difference between the groups was determined by t test or one-way analysis of variance. $P<0.05$ was considered statistically significant.

Results

The expression of KIF2C in different types of human cancers and its diagnostic and prognostic roles in GC

First, the expression profile of KIF2C in different kinds of human cancers was analyzed using the TIMER database. As illustrated in Fig. 1A, KIF2C was overexpressed in lymphoid neoplasm diffuse large b-cell lymphoma (DLBC), testicular germ cell tumors (TGCT), uterine carcinosarcoma (UCS), thymoma (THYM), cervical squamous cell carcinoma, and endocervical adenocarcinoma (CESC) tissues relative to their normal samples. Its expression was lower in bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC) samples compared to that in their corresponding normal samples. Furthermore, the upregulation of KIF2C expression was noted in STAD specimens when compared with their normal specimens (Fig. 1B and 1C). Moreover, KIF2C was found to be a potential diagnostic biomarker for GC, with an AUC of 0.931 (Fig. 1D). To investigate the prognostic potential of KIF2C in GC, Kaplan-Meier plotter was used. As shown in Fig 1E-G, the upregulation of KIF2C was associated with OS, DSS, and PFI in GC patients (OS HR=0.59, 95% CI=0.41 to 0.83, P=0.003; DSS HR=0.58, 95% CI=0.37 to 0.90, P=0.015; FPI HR=0.52, 95% CI=0.36 to 0.76, P=0.001), indicating that KIF2C can serve as a promising biomarker for diagnosis of GC.

The correlation between KIF2C and clinical characteristics of patients with GC

As displayed in Table 1, the upregulation of KIF2C was related to age (P=0.014), histological type (P=0.022), histological grade (P=0.017), antireflux treatment (P=0.004), but had no correlation with gender, TNM stage, pathologic stage, primary therapy outcome, residual tumor, or reflux history.

Table 1. The correlation between KIF2C and clinical characteristics of patients with gastric cancer

Characteristic	Low expression of KIF2C	High expression of KIF2C	p
n	187	188	
Age, mean ± SD	64.48±10.61	67.19±10.54	0.014
Gender, n (%)			0.617
Female	64 (17.1%)	70 (18.7%)	
Male	123 (32.8%)	118 (31.5%)	
T stage, n (%)			0.989
T1	9 (2.5%)	10 (2.7%)	
T2	40 (10.9%)	40 (10.9%)	
T3	86 (23.4%)	82 (22.3%)	
T4	50 (13.6%)	50 (13.6%)	
N stage, n (%)			0.909
N0	55 (15.4%)	56 (15.7%)	
N1	48 (13.4%)	49 (13.7%)	
N2	35 (9.8%)	40 (11.2%)	
N3	39 (10.9%)	35 (9.8%)	
M stage, n (%)			0.668
M0	163 (45.9%)	167 (47%)	
M1	14 (3.9%)	11 (3.1%)	
Pathologic stage, n (%)			0.966
Stage I	25 (7.1%)	28 (8%)	
Stage II	57 (16.2%)	54 (15.3%)	
Stage III	74 (21%)	76 (21.6%)	
Stage IV	19 (5.4%)	19 (5.4%)	
Primary therapy outcome, n (%)			0.122
PD	35 (11%)	30 (9.5%)	
SD	11 (3.5%)	6 (1.9%)	
PR	0 (0%)	4 (1.3%)	
CR	113 (35.6%)	118 (37.2%)	
Histological type, n (%)			0.022
Diffuse Type	40 (10.7%)	23 (6.1%)	
Mucinous Type	12 (3.2%)	7 (1.9%)	
Not Otherwise Specified	98 (26.2%)	109 (29.1%)	
Papillary Type	3 (0.8%)	2 (0.5%)	
Signet Ring Type	8 (2.1%)	3 (0.8%)	
Tubular Type	26 (7%)	43 (11.5%)	
Residual tumor, n (%)			0.962
R0	150 (45.6%)	148 (45%)	
R1	7 (2.1%)	8 (2.4%)	
R2	8 (2.4%)	8 (2.4%)	
Histologic grade, n (%)			0.017
G1	8 (2.2%)	2 (0.5%)	
G2	57 (15.6%)	80 (21.9%)	
G3	115 (31.4%)	104 (28.4%)	
Antireflux treatment, n (%)			0.004
No	63 (35.2%)	79 (44.1%)	
Yes	27 (15.1%)	10 (5.6%)	
Reflux history, n (%)			0.101
No	84 (39.3%)	91 (42.5%)	
Yes	25 (11.7%)	14 (6.5%)	

The correlation between KIF2C expression and immune infiltration

To investigate the relation between KIF2C expression and immune cell infiltration in GC, Spearman method was used. There was a positive correlation between the increased expression of KIF2C and the infiltration of Th2 cells, T helper cells, and aDC cells. However, the increased expression of KIF2C was inversely related to the infiltration of Mase cells, pDC cells, NK cells, and CD8 T cells, Tem cells, Tcm cells, and B cells in GC (Fig. 2A-G).

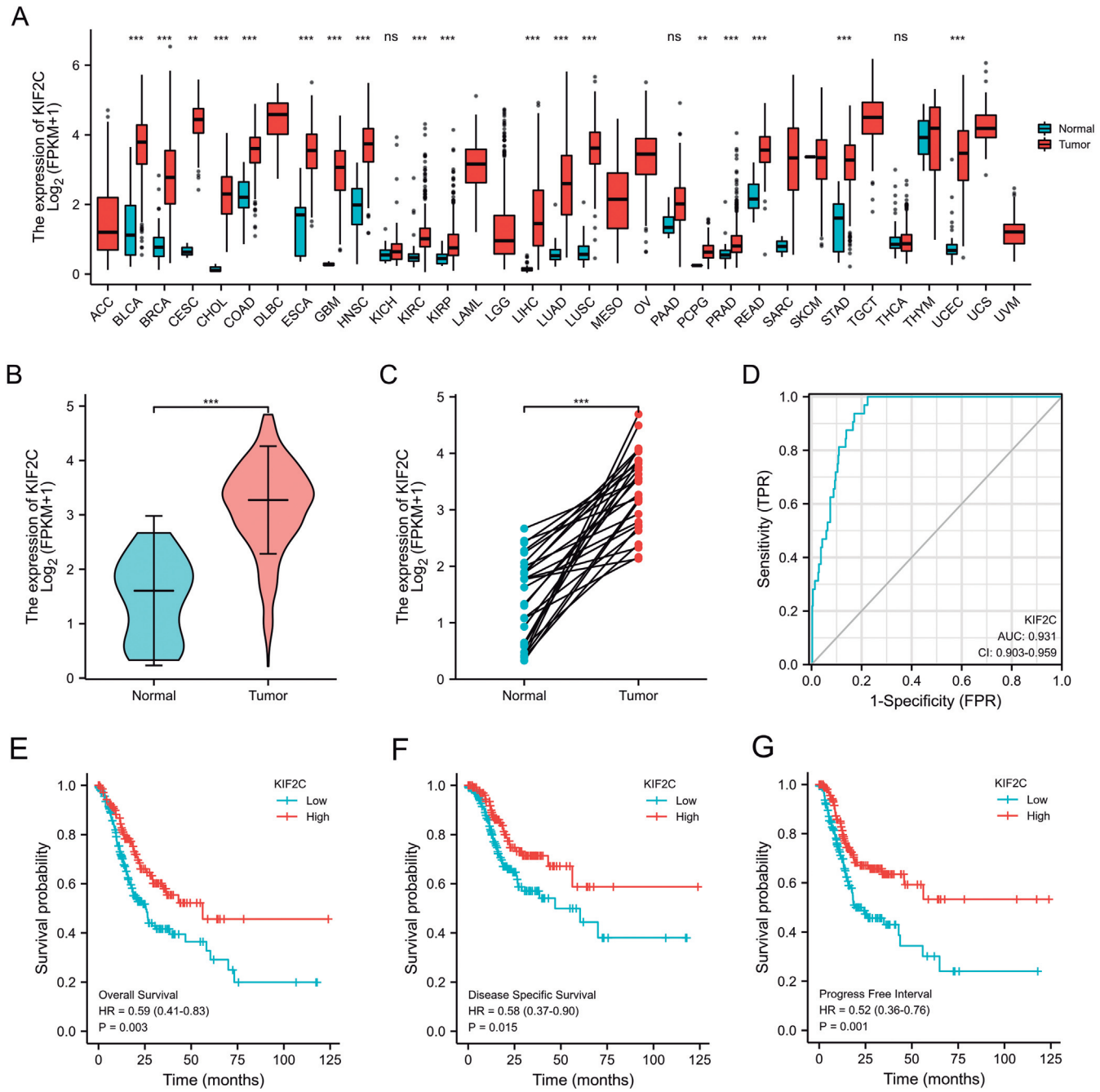

Fig. 1. KIF2C expression in different types of human cancers and its diagnostic and prognostic roles in GC. **A.** The expression of KIF2C in data sets of different cancer tissues relative to their normal tissues in the TIMER database. **B and C.** Comparison of KIF2C expression in normal tissue and STAD tissues. **D.** The ROC analysis of KIF2C expression was applied to distinguish STAD patients from non-STAD patients. **E-F.** Kaplan-Meier plotter was used to assess the relation between KIF2C expression and OS, DSS, and PFI in GC patients. ***P<0.001

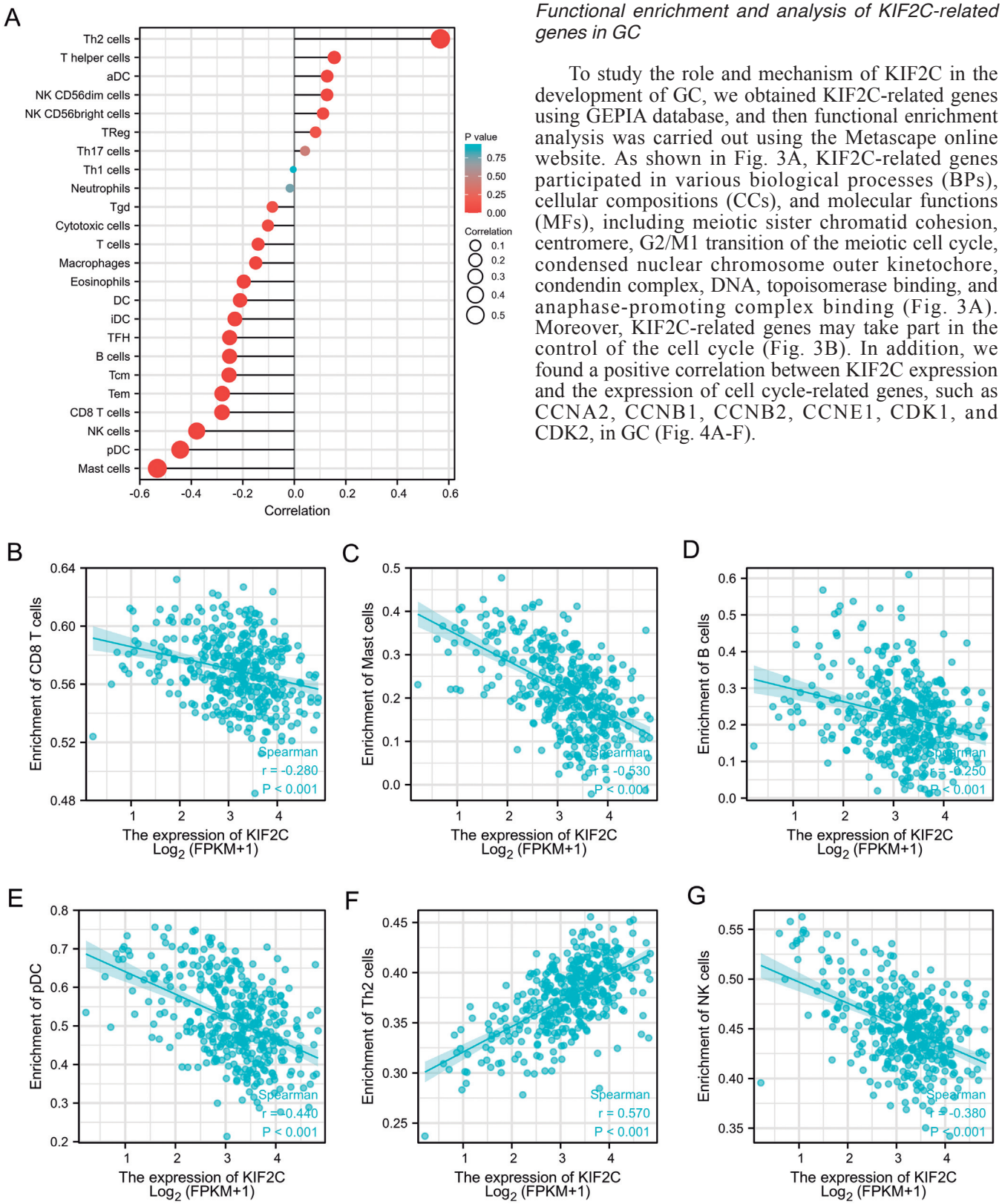

Fig. 2. The correlation between KIF2C expression and immune infiltration. **A.** The correlation between KIF2C expression and the infiltrating levels of immune cells in GC. **B.** KIF2C expression was negatively associated with the infiltration of Mase cells **(C)**, CD8 T cells **(B)**, B cells **(D)**, pDC cells **(E)**, and NK cells **(G)**, but was positively related with the infiltration levels of Th2 cells **(F)** in GC.

Functional enrichment and analysis of KIF2C-related genes in GC

To study the role and mechanism of KIF2C in the development of GC, we obtained KIF2C-related genes using GEPIA database, and then functional enrichment analysis was carried out using the Metascape online website. As shown in Fig. 3A, KIF2C-related genes participated in various biological processes (BPs), cellular compositions (CCs), and molecular functions (MFs), including meiotic sister chromatid cohesion, centromere, G2/M1 transition of the meiotic cell cycle, condensed nuclear chromosome outer kinetochore, condendin complex, DNA, topoisomerase binding, and anaphase-promoting complex binding (Fig. 3A). Moreover, KIF2C-related genes may take part in the control of the cell cycle (Fig. 3B). In addition, we found a positive correlation between KIF2C expression and the expression of cell cycle-related genes, such as CCNA2, CCNB1, CCNB2, CCNE1, CDK1, and CDK2, in GC (Fig. 4A-F).

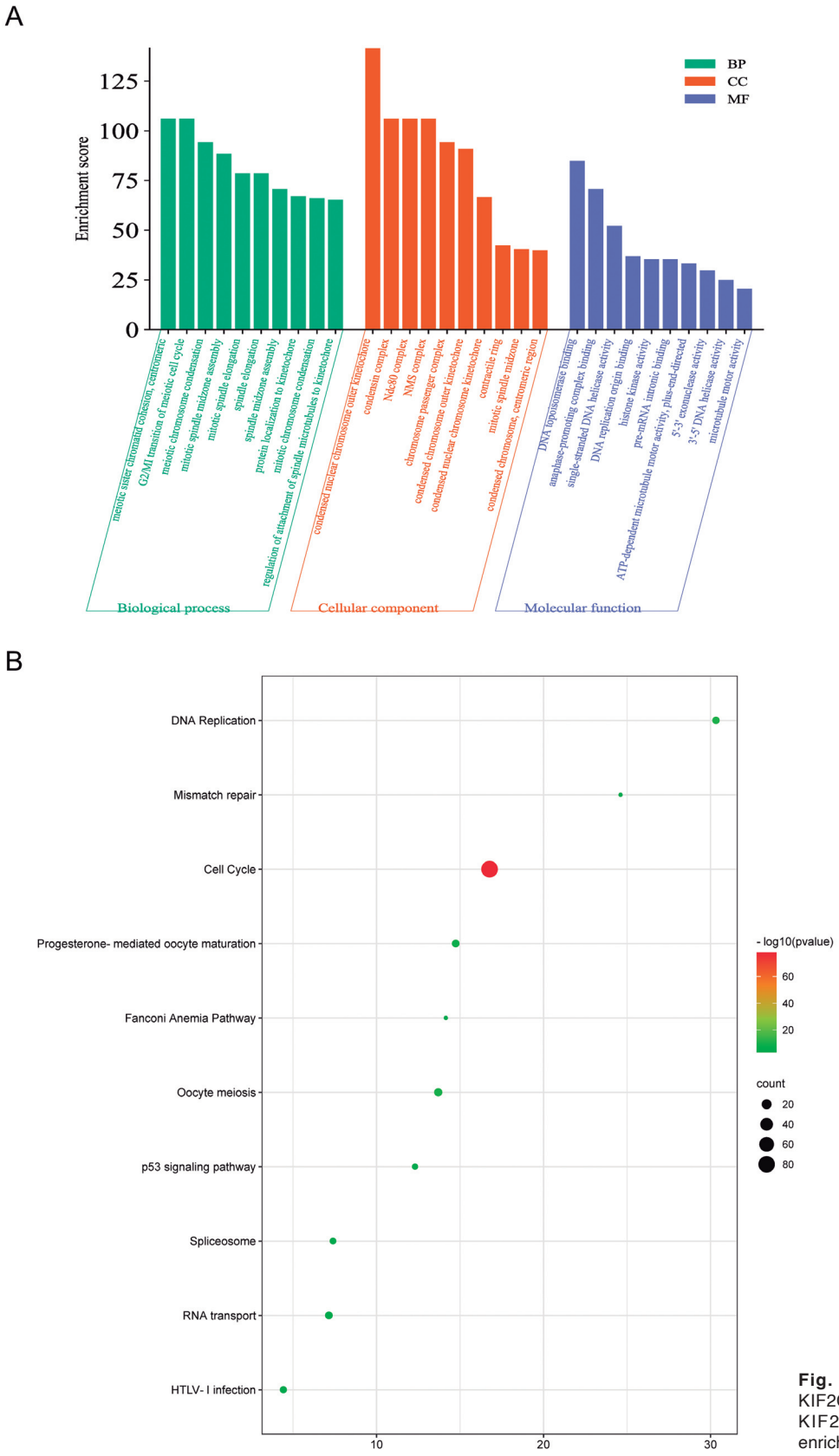

Fig. 3. Functional enrichment analysis of KIF2C in GC. **A.** GO enrichment analysis of KIF2C-related genes. **B.** KEGG pathway enrichment analysis of KIF2C-related genes.

KIF2C was upregulated in GC tissues

To further explain the impact of KIF2C in GC progression, the expression of KIF2C in GC specimens and their corresponding normal specimens was evaluated using RT-qPCR assay. As expected, in comparison with the normal specimens, KIF2C was overexpressed in GC specimens (Fig. 5A,B).

Silencing of KIF2C induces G0/G1 cell cycle arrest and inhibits cell proliferation in GC cells

The effect of KIF2C on tumor behavior was further validated *in vitro*. The expression of KIF2C in different cell lines was detected. As expected, the mRNA levels of KIF2C were significantly increased in GC cells (AGS, MKN-45, NCI-N87, and SNU-1) as compared with GES-1 cells (Fig. 6A). To explore the impact of KIF2C on GC cell cycle, KIF2C was knocked down in SNU-1 cells and overexpressed in AGS cells. As determined by western blot, KIF2C levels were decreased in SNU-1 cells transfected with small interfering RNA targeting KIF2C (si-KIF2C) compared with cells transfected with its negative control (si-NC). While, in comparison with pcDNA-transfected cells, KIF2C was upregulated in pcDNA-KIF2C-transfected AGS cells (Fig. 6B). The participation of KIF2C in the process of the cell cycle was validated using flow cytometry. As demonstrated in Fig. 6C, it was observed that the knockdown of KIF2C enhanced the distribution of G0/G1 phase and reduced the distribution of S phase in SNU-1 cells. Notably, KIF2C overexpression resulted in an opposite result in AGS cells (Fig. 6D). Furthermore, inhibition of KIF2C hindered the proliferation of SNU-1 cells, but overexpression of KIF2C increased the proliferation of AGS cells, as indicated by Edu assay (Fig. 6E,F).

Discussion

Many studies have been undertaken to explore a novel and effective treatment for GC, however, there is still a lack of a therapeutic approach for GC patients at advanced stage. So, there is a need for new and effective biomarkers and therapeutic targets for GC. Generally,

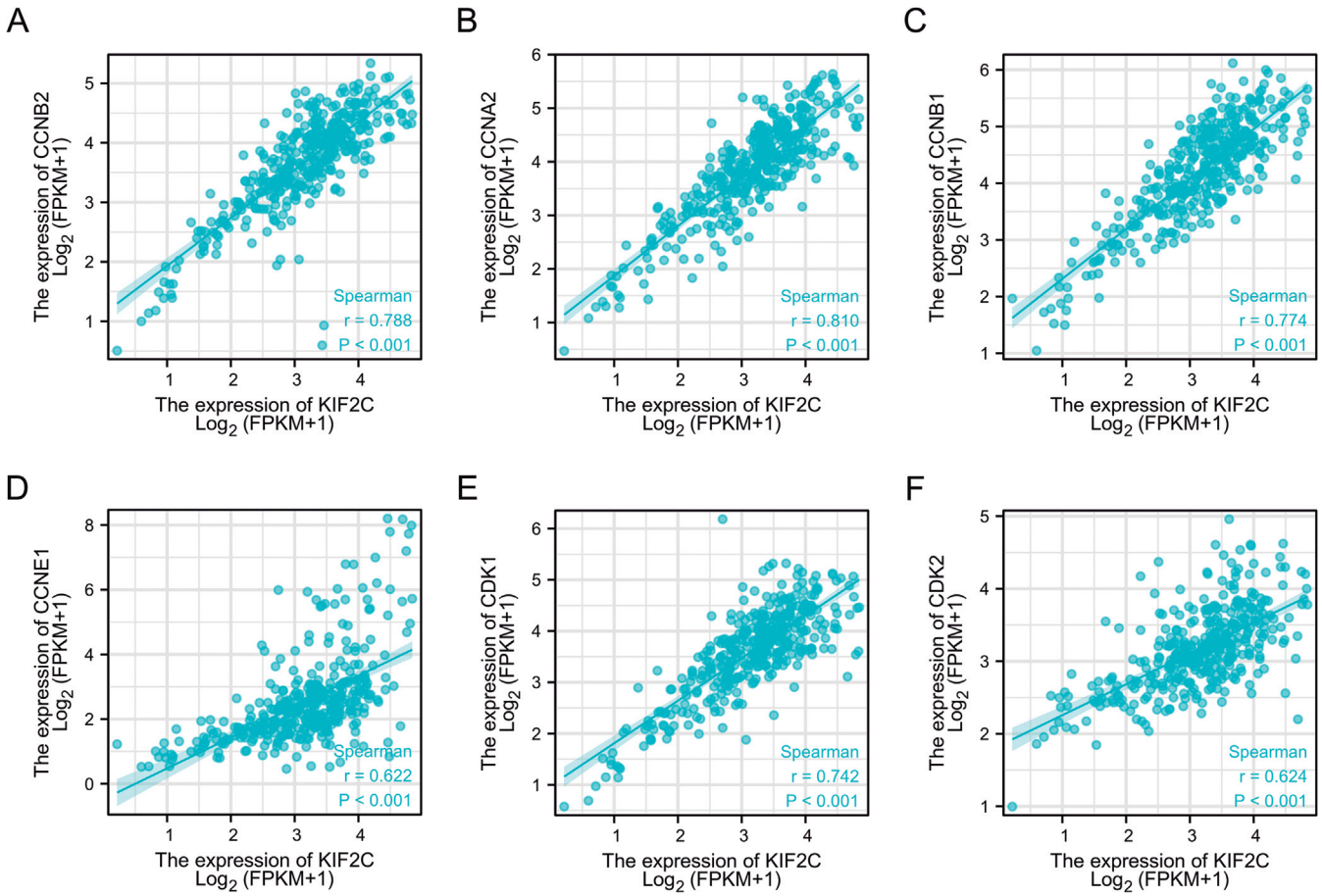

Fig. 4. KIF2C was related with the expression of cell cycle-related genes. Correlation analysis of KIF2C expression and CCNB2 **(A)**, CCNA2 **(B)**, CCNB **(C)**, CCNE1 **(D)**, CDK1 **(E)**, and CDK2 **(F)** levels in GC tissues.

tumor occurrence is accompanied by the alteration of DNA. DNA aneuploidy is considered as one of the important features of tumor cells and is a common form of chromosomal instability in tumor cells (Wenzel and Singh, 2018). Normally, cells have a functional regulatory mechanism that maintains the normal replication and separation of chromosomes by strictly controlling the orderly alternation of the cell cycle. Once a step in this regulation mechanism goes wrong, it is most likely to lead to chromosome mis-replication and mis-segregation, and the abnormal expression of genes associated with the cell cycle, thereby resulting in tumorigenesis (Bakhoum and Cantley, 2018). Chromosome mis-replication and mis-segregation are recognized as the leading cause of chromosomal instability in tumor cells. Thus, targeting mitosis is considered as a potential therapeutic approach for GC (Liu et al., 2019).

KIF2C is considered an important regulator of chromosome segregation, which is crucial for mitosis (Gwon et al., 2012). Abnormal expression of KIF2C disrupts the process of mitosis, which is considered a potential cause of the occurrence of human cancer. Previously, Gan et al. demonstrated that KIF2C functioned as a promising biomarker for the diagnosis of non-small cell lung cancer, moreover, it functioned as a target of microRNA (miR)-325-3p to promote the growth of non-small cell lung cancer cells, revealing the oncogenic role of KIF2C (Gan et al., 2019). Wei et al. suggested that KIF2C functioned as a target of the wingless and int-1/β-catenin pathway to mediate the crosstalk between Wnt/β-catenin and mammalian target of rapamycin complex 1 signaling, as well as boost the proliferative, migratory, and invasive capacity of hepatocellular carcinoma cells in vitro and in vivo (Wei et al., 2021). Moreover, the oncogenic role of KIF2C was also validated by Gao et al. (2021). In bladder cancer, upregulation of KIF2C, induced by the circRGNEF/miR-548 axis, facilitated the growth of bladder cancer cells (Yang et al., 2020). However, the potential function of KIF2C in GC development remains unclear. Herein, we discovered that KIF2C was upregulated in multiple tumors, including GC, and was associated with poor survival time of GC patients, thereby presenting the prognostic role of KIF2C in GC. To further show the role of KIF2C in GC development, we obtained KIF2C-related genes using GEPIA database, and then analyzed them using Metascape online website. The results suggested the participation of KIF2C in the process of the cell cycle. Moreover, silencing of KIF2C induced cell cycle arrest and inhibited the proliferative ability of GC cells, implying that KIF2C plays an oncogenic role in GC development.

The immune system is one of the leading ways that protect against tumor cells in the body, and immunotherapy is a promising method to treat GC. For this reason, enhancing the host immunity to kill tumor cells is a pivotal strategy for GC therapy (Dominguez-Brauer et al., 2015). There is now increasing evidence to show that KIF2C goes hand in hand with host immunity (Lu et al., 2014). For example, KIF2C was upregulated in endometrial cancer, and its knockdown can prolong the G1 phases and repress the progression of endometrial tumor cells, as well as restraining the apoptosis of CD8 T cells. These findings suggest that KIF2C is associated with tumor immune infiltration, has a tumor-promoting role, and might be used as a prognostic biomarker for endometrial cancer (An et al., 2021). Additionally, it was found that the upregulation KIF2C had a direct correlation to the reduced immune infiltration in LUAD (Zeng et al., 2020). Nevertheless, if there is a link between the overexpression of KIF2C and immune infiltration in GC it has never been established. Herein, we discovered a positive association between KIF2C expression and the infiltration of Th2 cells, T helper cells and aDC cells. KIF2C expression was negatively associated with the infiltration of Mase cells, pDC cells, NK cells, CD8 T cells, Tem cells, Tcm cells, and B cells in GC. This conclusion is in line with a recent study, which demonstrated that KIF2C is a potential biomarker for immune infiltration and is a target for non-small cell lung cancer treatment (Chen et al., 2021).

Conclusion

In conclusion, our data implied that KIF2C was upregulated in GC and might be used as a promising biomarker for diagnosis and prediction of prognosis of

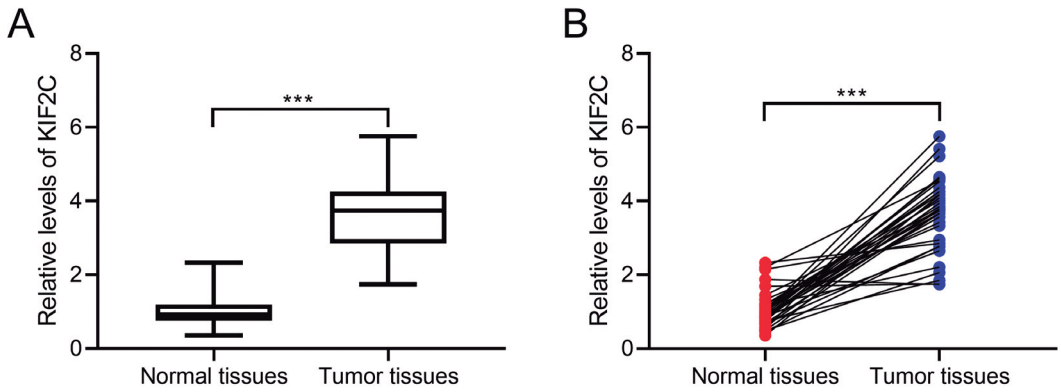

Fig. 5. KIF2C was upregulated in GC tissues. **A and B.** RT-qPCR analysis of KIF2C levels in normal and GC tissues. ***P<0.001.

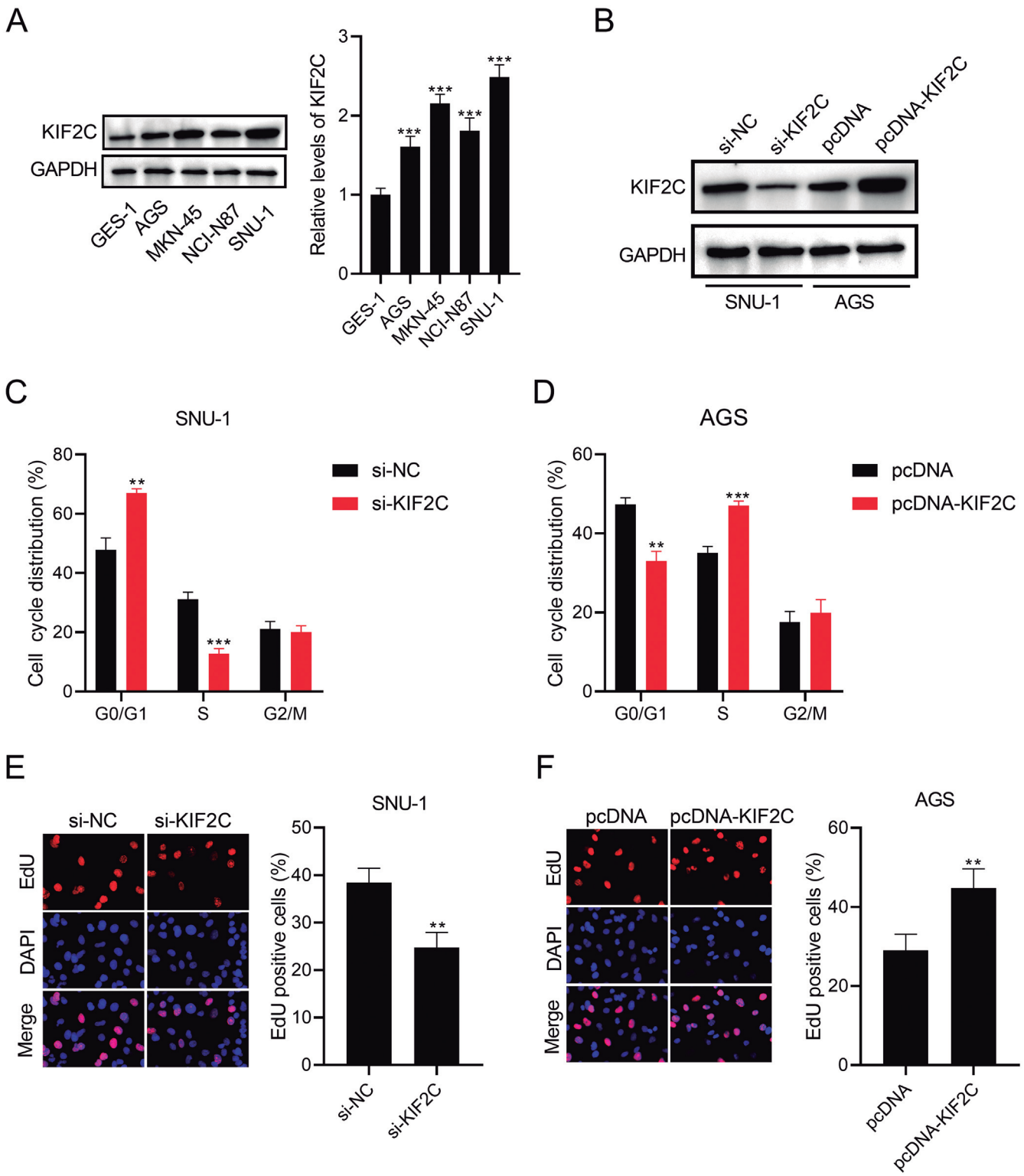

Fig. 6. Knockdown of KIF2C inhibited the proliferation of GC cells. **A.** RT-qPCR analysis of KIF2C expression in human normal gastric mucosa cells (GES-1) and GC cell lines. **B.** Western blot was conducted to evaluate the levels of KIF2C in AGS and SNU-1 cells. **C and D.** Flow cytometry was used to determine the role of KIF2C in GC cell cycle. **E and F.** EdU assay was carried out to assess the role of KIF2C in the proliferation of AGS and SNU-1 cells. ***P*<0.01, ****P*<0.001.

GC. More importantly, KIF2C correlated with immune infiltration in GC and its silencing can hinder the proliferation of GC cells by inducing G0/G1 phase cell cycle arrest. This shows that KIF2C might act as a potential therapeutic target for GC. With further experiments investigating the downstream signaling of KIF2C in GC development, we may come to fully appreciate the function of KIF2C in the future. More in-depth research will provide the experimental basis for KIF2C to become a target of GC gene therapy.

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Declaration of interest. The authors declare that they have no conflict of interest.

Authors' contributions. Shuai Li and Xinfang Hou designed the study. Shuai Li and Yulian Ma performed the experiments. Chen Wu analyzed the data. The first draft of the manuscript was written by Shuai Li, and all authors commented on previous versions of the manuscript. Xinfang Hou read and approved the final manuscript.

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Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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