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Has_circ_0071803 promotes colorectal cancer progression by regulating miR-330-5p/MAPK signaling pathway

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Summary. Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. A lack of effective targeted therapies against CRC makes the treatment challenging. Here, we report a circular RNA (circRNA), has_circ_0071803, functioning as an oncogene in CRC. Circ_0071803 was upregulated in CRC tissues and cell lines, and its expression levels were inversely correlated with the prognosis and survival rate of patients with CRC. Circ_0071803 knockdown suppressed cell proliferation, migration, and invasion in CRC. Moreover, we found that circ_0071803 sponged miR-330-5p, thereby upregulating mitogen-activated protein kinase 1 (MAPK1) in CRC cells. The suppression of cell activities by circ_0071803 knockdown were rescued by miR-330-5p inhibition or MAPK1 overexpression. Collectively, our findings elucidate that circ_0071803 promotes CRC progression by regulating the miR-330-5p/MAPK1 pathway, providing potential therapeutic targets for designing effective targeted treatments.

Key words: Colorectal cancer, Circ_0071803, MiR-330-5p/MAPK1, Proliferation, Metastasis

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed malignant diseases worldwide, with more than 600,000 new cases and 90,000 deaths annually (Brenner et al., 2014; Dekker et al., 2019). Although some advances in the diagnosis and treatment of CRC have been made over the last decade, CRC still remains aggressive and resistant to existing drugs with early onset age, high probability of recurrence and distant metastasis, and poor overall survival of patients (Keum and Giovannucci, 2019). It is, therefore, imperative to discover new molecular targets involved in CRC progression to provide scientific resources for drug development (Li et al., 2021).

Endogenous non-coding RNAs play multifaceted roles in the development and progression of malignant tumors (Chen and Shan, 2021). Circle RNAs (circRNAs) are a novel type of non-coding RNAs (ncRNAs). They are generated by a back-splicing event from exons of genes, resulting in a covalently closed loop that prevents exonuclease degradation. In general, circRNAs act as transcriptional regulators to modulate the expression of downstream genes, playing vital roles in cellular physiology (Lei et al., 2020). Consequently, dysregulation of circRNA is closely associated with cancer progression and therapeutic resistance (Cui et al., 2020). For example, circRNA-SORE is upregulated in sorafenib-resistant cancer cells (Xu et al., 2020), and circRNA-ASPA1 is critical for the resistance of glioblastoma to temozolomide (Wei et al., 2021). Therefore, characterization of circRNAs that contribute to cancer progression and drug resistance has far-reaching biological and clinical significance for cancer treatment. Has_circ_0071803 is a novel circRNA, and its biological function in human cancers has not yet been explored.

CircRNAs epigenetically modulate gene expression by sponging microRNAs (miRNAs) that bind to the 3'-untranslated region of mRNAs or to initiate mRNA degradation or to repress translation. One miRNA, miR-330-5p, has been widely implicated in cancer progression and therapeutic resistance. It has been observed that the expression of miR-330-5p is dysregulated in many different cancer types, including lung, prostate, breast, and colorectal cancers (Jafarzadeh et al., 2022). In bladder cancer, miR-330-5p is sponged by circ_0008532, thereby regulating the expression of the MTGR1/NOTCH pathway and promoting tumor progression (Chen et al., 2020). Additionally, miR-330-

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5p is sponged by a tumor-suppressive circular RNA, CircITCH, which alleviates doxorubicin-induced cardiotoxicity (Han et al., 2020). Moreover, miR-330-5p dysregulation renders the downstream molecules dysfunctional, such as ITGA5 (Yoo et al., 2016), LASP1 (Lu et al., 2020), and UBA2 (Guo et al., 2021), facilitating CRC progression and metastasis.

Here we find that circ_0071803 can sponge miR-330-5p, which leads to the upregulation of MAPK1. Moreover, either miR-330-5p knockdown or MAPK1 overexpression can reverse the phenotype of CRC cells with circ_0071803 knockdown. Taken together, this study demonstrates that circ_0071803 promotes CRC progression by sponging miR-330-5p and upregulating MAPK1, providing a new potential therapeutic target for developing new targeted therapies.

Materials and methods

Cell culture

Four human CRC cell lines (SW620, HT-29, HCT116, and LoVo) and a human normal colon cell line (NCM460) were obtained from the Cell Bank of the Type Culture Collection, Chinese Academy of Sciences (Shanghai, China). The cells were cultured in DMEM (#L110; BasalMedia Biotech Co., Ltd, Shanghai, China) supplemented with 10% fetal bovine serum (#FSP500; ExCell Biol) and 1% penicillin-streptomycin (#S110B; BasalMedia Biotech Co., Ltd, Shanghai, China) in a 5% CO_2 incubator at 37°C.

Human tissues

All experimental procedures were approved by the Research Ethics Committee of the First Hospital of Jiaxing and were performed in accordance with the ethical guideline of the Declaration of Helsinki. Informed consent was obtained from all participants. The CRC tissues and paired adjacent normal tissues were obtained from the First Hospital of Jiaxing.

Cell viability and colony formation assays

After digestion, cells were seeded into 96-well plates at a density of 1000 cells/well. The cell viability assay was carried out using a CCK-8 kit (#40203ES92; Yeasen Biotech Co., Ltd, Shanghai, China) by adding 10 μL of CCK-8 solution to each well. The absorbance at 450 nm (A450) was measured at indicated times. For the colony formation assay, cells were seeded into six-well plates at a density of 1000 cells/well and then were cultured for 14 days. Subsequently, cell clones were fixed with methanol for 30 minutes and then stained with crystal violet for 1h before counting.

Cell migration and invasion assays

A total of 2~5×10^4 cells were resuspended in the fetal bovine serum-free medium in the upper chamber coated with (invasion) or without (migration) matrigel (#354480 and #353097; Corning, NY, USA). The medium containing fetal bovine serum was added to the lower chamber. After 24h of incubation, cells were fixed with methanol and stained with crystal violet before counting.

Bioinformatics analysis

The Gene Expression Omnibus (GEO) database (GSE172229) was used to identify the dysregulated circRNAs in CRC. The circular RNA interactome database (http://circinteractome.nia.nih.gov/Circular_RNA/circular rna.html) was employed to predict the binding between circ_0071803 and miR-330-5p, and the Starbase database (http://starbase.sysu.edu.cn/) was employed to predict the binding between miR-330-5p and MAPK1.

RNA extraction and real-time polymerase chain reaction (RT-qPCR)

TRIzol reagent (#15596018; Invitrogen, USA) was used to extract total RNAs from cells and tissues. cDNAs were obtained by reverse-transcription from the isolated RNAs using HiScript III-RT SuperMix (#R323-01; Vazyme) and a PrimeScriptTM RT reagent kit (#RR037A; Takara, Shiga, Japan). RT-qPCR analyses were performed using Chamq Universal SYBR qPCR Master Mix (#Q711-03; Vazyme Biotech Co., Ltd, Jiangsu, China,). The relative gene expression levels were calculated using the $2^{-\Delta\Delta CT}$ method.

RNA-binding protein immunoprecipitation (RIP) assay

The RIP assay was carried out using a RIP assay Kit (#RN1005; Life Sciences, USA) in accordance with the manufacturer's instructions. Argonaute 2 (Ago2) antibody was obtained from MBL International (#RN003M). Immunoprecipitated RNAs were collected using phenol-chloroform extraction. The collected RNAs were then used for reverse transcription and RT-qPCR analysis.

siRNAs transfection and DNA constructs

Small interfering RNAs (siRNAs) targeting circ_0071803 were custom synthesized by GenePharma Co., Ltd (Shanghai, China). The miR-330-5p inhibitor vector was constructed by Genechem Co., Ltd (Shanghai, China). The plasmid encoding MAPK1 was purchased from Vigene Bioscience (Rockville, MD, USA) and subcloned into lentiviral vectors. The constructs were transfected into cells using Neofect DNA transfection reagent (#TF201201; Tengyi Biotech Co., Ltd Shanghai, China). After 48h of transfection, the supernatant was collected to infect cells with 8 μg/mL polybrene (#H9268; Sigma, St Louis, MO, USA). After

infection, cells were selected using 0.5 mg/mL G418 (#A600958-0005; Sangon Biotech, Shanghai, China) for 1-2 weeks. The siRNAs were transfected into cells using Lipofectamine 2000 transfection reagent (#11668019; Invitrogen, USA).

Immunoblotting

For immunoblotting, cells were lysed by the RIPA buffer. Crude proteins were quantified using the bicinchoninic acid (BCA) assay. Proteins were separated by SDS-PAGE electrophoresis and then were transferred to a PVDF membrane (#IPVH00010; Millipore, Billerica, MA, USA). The membrane was blocked with 5% BSA (#V900933-1KG; Sigma-Aldrich, MO, USA) for 30 min at room temperature followed by incubation with primary antibodies, including MAPK1 (1:1000; #ab32081; Abcam Cambridge, MA, USA), P-ERK1/2 (1:1000; #4370; Cell Signaling Technology, Beverly, MA, USA), ERK1/2 (1:1000; #4695; Cell Signaling Technology, Beverly, MA, USA), and GAPDH (1:1000; #2118; Cell Signaling Technology, Beverly, MA, USA), overnight at 4°C. After three washes with 1×PBS, the membrane was incubated with secondary antibodies (1:3000; #7074V; Cell Signaling Technology, Beverly, MA, USA). Finally, the protein bands were visualized using an enhanced chemiluminescence (ECL) system.

Statistical analyses

All data were plotted as mean ± standard deviation (SD). Statistical analysis was conducted using the SPSS 22.0 software (IBM Corp, Armonk, NY, USA). Data between two independent groups were compared using Student's t-test, and multiple groups were compared using one-way ANOVA. Categorical data were evaluated by Chi-square distribution (χ^2). The correlations between gene expression levels and cell phenotypes were assessed with KM-Plot and Pearson's analysis. $P<0.05$ was considered statistically significant. *, **, and *** represented $P<0.05$, $P<0.01$, and $P<0.001$, respectively.

Results

Circ_0071803 is upregulated in CRC and circ_0071803 upregulation predicts poor prognosis

To find the circRNAs involved in CRC progression, we first screened dysregulated circRNAs in CRC in the GEO database (GSE172229). The screen revealed that circ_0071803 was markedly upregulated in CRC relative to primary normal samples (Fig. 1A). We then examined the expression levels of circ_0071803 in human CRC tissues by RT-qPCR. Circ_0071803 expression in CRC tissues was significantly higher than that in adjacent health tissues (Fig. 1B). Furthermore, KM-Plot analysis showed that circ_0071803 expression levels were reversely correlated with the survival rates of CRC patients (Fig. 1C). To confirm the upregulation of circ_0071803 in CRCs further, we assessed the expression level of circ_0071803 in CRC cell lines by RT-qPCR. We found that circ_0071803 was upregulated in all CRC cell lines tested (SW620, HT-29, HCT116, and LoVo) compared to the human normal colon cell line (NCM460) (Fig. 1D). Moreover, we found that the GAPDH mRNA was digested by RNAase, but circ_0071803 was not, indicating that the structure of circ_0071803 is circular without 5′ and 3′ ends (Fig. 1E). Altogether, these results suggest that circ_0071803 is upregulated in CRC tissues and cells, which is correlated with the low survival rate of patients with CRC.

Knockdown circ_0071803 inhibits CRC cell proliferation, migration, and invasion

Having demonstrated the upregulation of circ_0071803 in CRC tissues and cell lines, we set out to investigate how circ_0071803 affects CRC progression. First, we knocked down the expression of endogenous circ_0071803 in HT-29 and HCT116 cell lines using specific siRNAs. RT-qPCR confirmed the knockdown of circ_0071803 expression in CRC cells (Fig. 2A). Cell viability and colony formation assays showed that circ_0071803 knockdown attenuated cell viability (Fig. 2B) and colony formation (Fig. 2C) of HT-29 and HCT116 cells. Besides, we detected the expression level of PCNA in CRC cells by Western blot (Fig. 2D). The results showed that circ_0071803 silence could significantly reduce PCNA expression, indicating that circ_0071803 knockdown can attenuate the proliferation of HT-29 cells. Furthermore, cell migration and invasion assays revealed that circ_0071803 knockdown suppressed the migratory and invasive potential of HT-29 and HCT116 cells (Fig. 2E,F). Taken together, these results suggest that circ_0071803 plays an oncogenic role in CRC progression.

Circ_0071803 regulates MAPK1 expression by sponging miR-330-5p in CRC cells

To identify the downstream target of circ_0071803, we screened the circular RNA interactome for miRNA(s) that could bind to circ_0071803. The screen revealed that circ_0071803 contained a putative binding site for miR-330-5p (Fig. 3A). Similarly, we used the starbase database to predict the target gene of miR-330-5p and found MAPK1 as the putative target gene (Fig. 3A). The RIP assay showed that circ_0071803, miR-330-5p, and MAPK1 all could bind to the AGO2 protein, implying the interactions between them (Fig. 3B). Next, we examined how the interactions between circ_0071803, miR-330-5p, and MAPK1 modulated the functions of each other. To this end, we first determined whether circ_0071803 regulates the expression of miR-330-5p and MAPK1. Notably, knockdown of circ_0071803 in both HT-29 and HCT116 cell lines significantly increased the expression of miR-330-5p, while

decreasing the expression of MAPK1 (Fig. 3C). Next, we wondered whether miR-330-5p and MAPK1 were dysregulated in CRC cell lines and tissues. qRT-PCR quantification showed that miR-330-5p was downregulated, whereas MAPK1 was upregulated in the four CRC cell lines (SW620, HT-29, HCT116, and LoVo) compared with the expression in the human normal colon cell line (NCM460) (Fig. 3D). Similarly, miR-330-5p was downregulated, whereas MAPK1 was upregulated in the CRC tissues compared with the normal tissues (Fig. 3E). Moreover, Pearson's analysis showed that miR-330-5p expression was negatively correlated with, while MAPK1 expression was positively correlated with circ_0071803 expression (Fig. 3F). Collectively, these results indicate that circ_0071803 promotes MAPK1 expression by sponging miR-330-5p.

Circ_0071803 promotes cell proliferation, migration, and invasion in CRC by regulating miR-330-5p/MAPK signaling axis

To validate that circ_0071803 plays oncogenic roles in CRC progression through regulating the miR-330-5p/MAPK axis, we inhibited miR-330-5p expression or increased MAPK1 expression in the CRC cell lines with circ_0071803 knockdown. The results showed that both miR-330-5p inhibition and MAPK1 overexpression

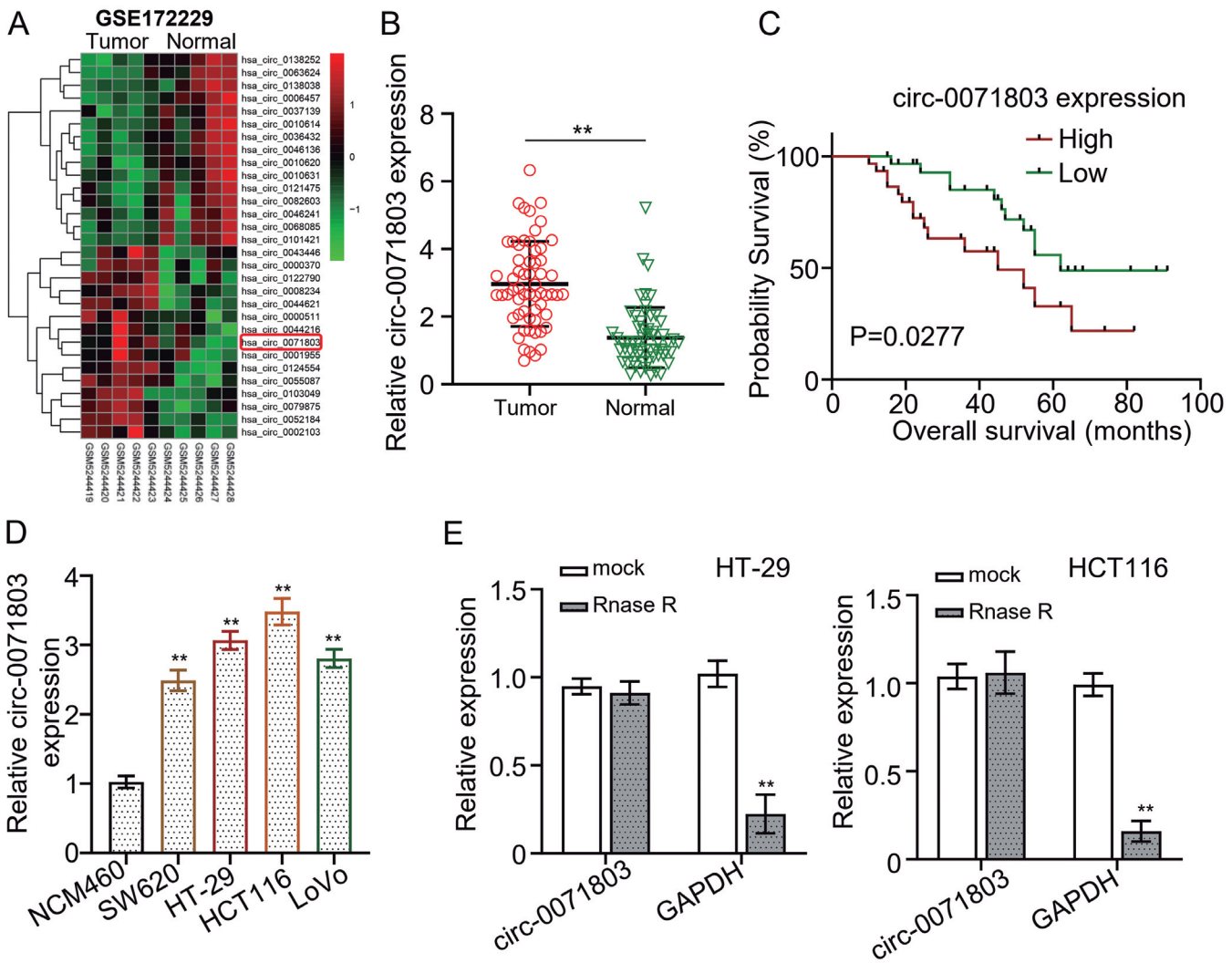

Fig. 1. Circ_0071803 is upregulated in CRC and circ_0071803 overexpression predicts poor prognosis. **A.** Top 15 upregulated and downregulated circRNAs in CRC tissues as revealed by an analysis of GEO dataset GSE172229. **B.** RT-qPCR quantifying the expression level of circ_0071803 in 60 pairs of CRC tissues and adjacent normal tissues. **C.** KM-Plot curves showing the correlation between the expression of circ_0071803 and the survival rate of patients with CRC. **D.** RT-qPCR assessing the expression level of circ_0071803 in four CRC cell lines (SW620, HT-29, HCT116, and LoVo) and a human normal colon cell line (NCM460). **E.** RT-qPCR assessing the expression levels of circ_0071803 and GAPDH in HT-29 and HCT116 cell lines after RNAase R treatment for 30 min. ***P*<0.01.

significantly increased MAPK1 expression levels in circ_0071803 knockdown cell lines (Fig. 4A). Consistent with the RT-qPCR results, the protein level of MAPK1 was significantly increased in circ_0071803 knockdown cells co-transfected with miR-330-5p inhibitors or pcDNA-MAPK1 (Fig. 4B). *In vitro*

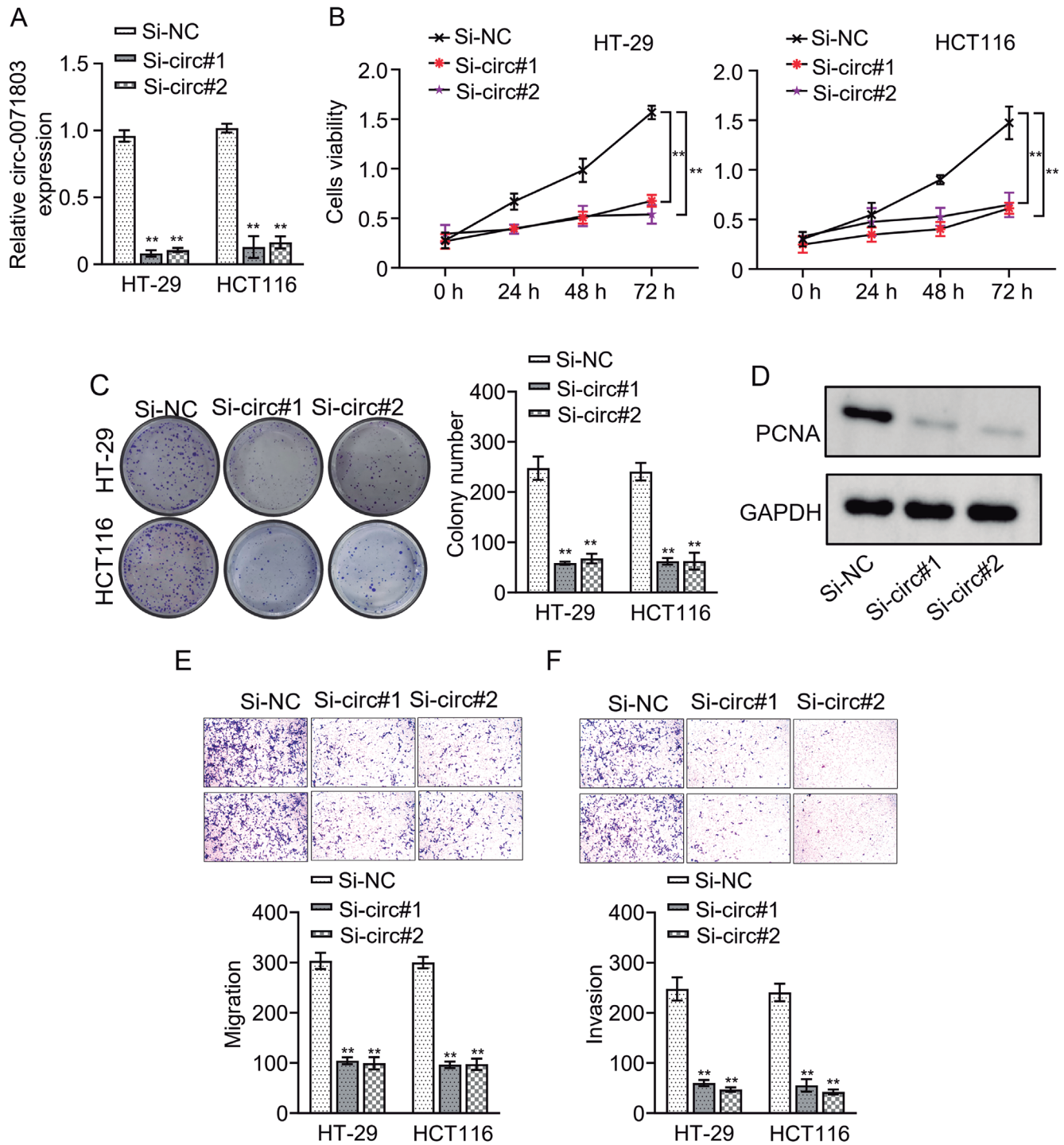

Fig. 2. Circ_0071803 knockdown inhibits CRC cell proliferation, migration, and invasion. **A.** RT-qPCR validating the knockdown of circ_0071803 in HT-29 and HCT116 cell lines. **B, C.** CCK-8 **(B)** and colony formation **(C)** assays examining the cell proliferation of T-29 and HCT116 cell lines after circ_0071803 knockdown. **D.** The expression level of PCNA in CRC cells was detected by Western blot. **E, F.** Transwell migration **(E)** and invasion **(F)** assays examining the migration and invasion of T-29 and HCT116 cell lines after circ_0071803 knockdown. $^{**}P<0.01$.

functional analyses revealed that either miR-330-5p inhibition or MAPK1 upregulation reversed the tumor-suppressive effects of circ_0071803 knockdown, including colony formation and cell migration and invasion. (Fig. 4C,D). These results suggest that circ_0071803 promotes CRC progression through regulating the miR-330-5p/MAPK signaling pathway.

Discussion

In this study, we report the involvement of the circ_0071803/miR-330-5p/MAPK signaling axis in CRC progression. Emerging evidence has shown that the abnormal expression of circRNAs, such as circNSUN2 (Zhang et al., 2019), circ_001680 (Jian et al., 2020),

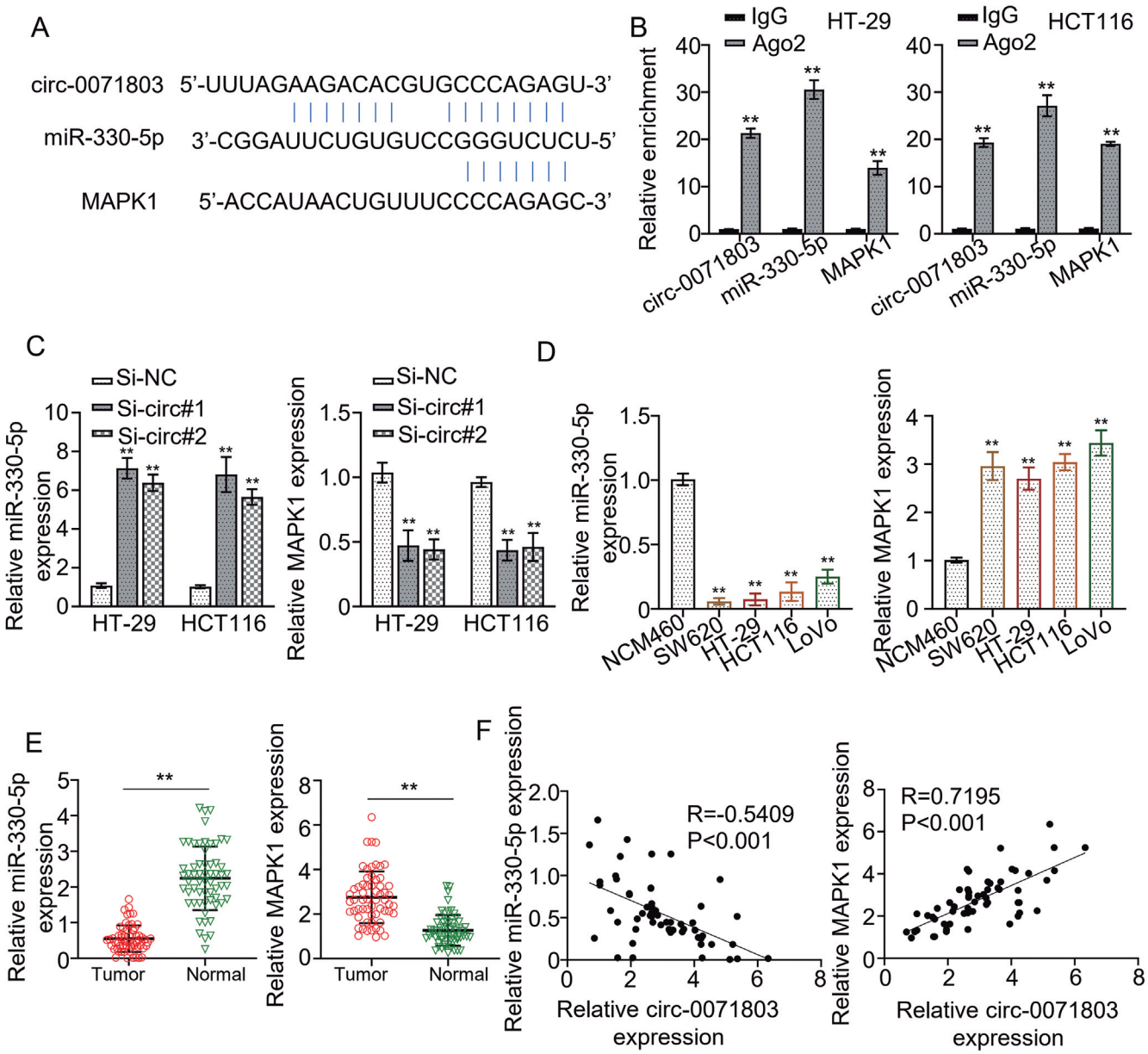

Fig. 3. Circ_0071803 regulates MAPK1 expression by sponging miR-330-5p in CRC cells. **A.** Predicted binding sites of circ_0071803, miR-330-5p, and MAPK1. **B.** RIP assay showing the relative enrichment of circ_0071803, miR-330-5p and MAPK1 in T-29 and HCT116 cell lines. **C.** RT-qPCR quantifying the expression levels of miR-330-5p and MAPK1 in T-29 and HCT116 cell lines after circ_0071803 knockdown. **D.** RT-qPCR analyzing the expression levels of miR-330-5p and MAPK1 in four CRC cell lines (SW620, HT-29, HCT116, and LoVo) and a human normal colon cell line (NCM460). **E.** RT-qPCR quantifying the expression levels of miR-330-5p and MAPK1 in 60 pairs of CRC and adjacent normal tissues. **F.** Pearson's analysis of the correlation between the expression levels of circ_0071803 and miR-330-5p, and between the expression levels of miR-330-5p and MAPK1 in CRC tissues. ***P*<0.01.

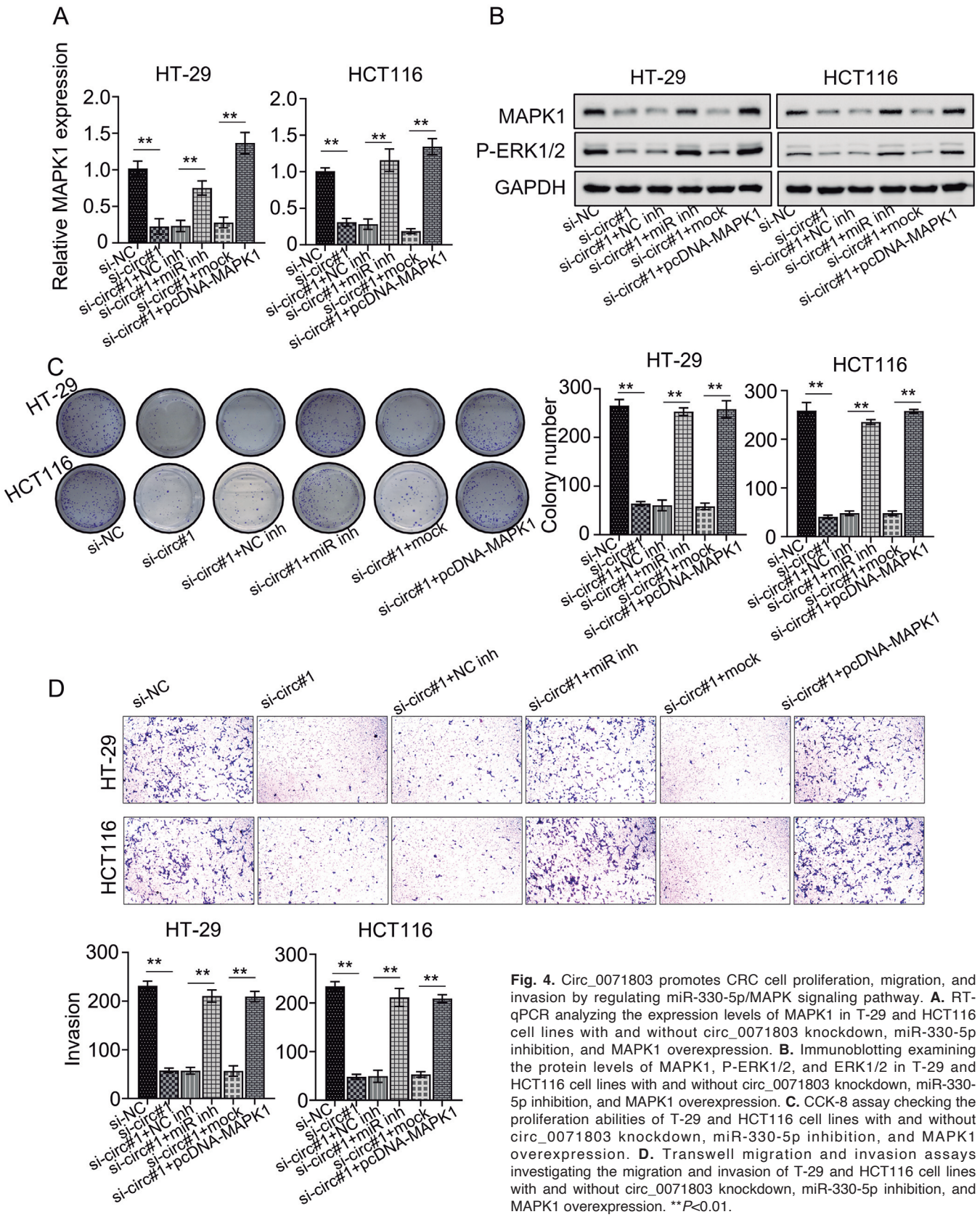

Fig. 4. Circ_0071803 promotes CRC cell proliferation, migration, and invasion by regulating miR-330-5p/MAPK signaling pathway. **A.** RT-qPCR analyzing the expression levels of MAPK1 in T-29 and HCT116 cell lines with and without circ_0071803 knockdown, miR-330-5p inhibition, and MAPK1 overexpression. **B.** Immunoblotting examining the protein levels of MAPK1, P-ERK1/2, and ERK1/2 in T-29 and HCT116 cell lines with and without circ_0071803 knockdown, miR-330-5p inhibition, and MAPK1 overexpression. **C.** CCK-8 assay checking the proliferation abilities of T-29 and HCT116 cell lines with and without circ_0071803 knockdown, miR-330-5p inhibition, and MAPK1 overexpression. **D.** Transwell migration and invasion assays investigating the migration and invasion of T-29 and HCT116 cell lines with and without circ_0071803 knockdown, miR-330-5p inhibition, and MAPK1 overexpression. ***P*<0.01.

circ1662 (Chen et al., 2021), and circ3823 (2021), plays a key role in tumorigenesis and malignant transformation of CRC. For instance, circMYH9 drives CRC proliferation by promoting serine/glycine metabolism and maintaining redox homeostasis (Liu et al., 2021). Considering their versatile roles in CRC progression, functional investigations of circRNAs and the relevant molecular mechanisms in cancer development and progression are the key to identify new therapeutic targets for developing cancer therapies. In this study, we provided the first evidence that circ_0071803 was highly expressed in CRC cells and tissues, promoting the proliferation, migration, and invasion of CRC cells.

CircRNAs typically sponge miRNAs to modulate the expression of targeted downstream genes in human cancers. For example, circRNF20 sponges miR-487a to enhance the Warburg effect, also known as aerobic glycolysis, in breast cancer (Cao et al., 2020). In CRC, circHERC4 sponges miR-556-5p to activate the CTBP2/E-cadherin pathway, thereby promoting tumor metastasis (He et al., 2021). In this study, we found that circ_0071803 sponged miR-330-5p and negatively regulated miR-330-5p expression (Fig. 3). Down-regulation of miR-330-5p has been found in various cancer types including non-small-cell lung carcinoma (Cui et al., 2018), melanoma (Su et al., 2016), ovarian cancer (Shao et al., 2018), and cervical cancer (Zhao et al., 2019), contributing to multiple malignant phenotypes. For example, miR-300-5p inhibits the progression of epithelial ovarian cancer through modulating MAPK signaling, and its downregulation results in cisplatin resistance (Lin et al., 2018). On the other hand, in hepatocellular carcinoma, miR-330-5p is upregulated and suppresses SPRY2 expression, which promotes cell proliferation via activating the MAPK/ERK signaling (Xiao et al., 2018). Similarly, miR-330-5p overexpression leads to ERK activation in non-small-cell lung carcinoma (Wang et al., 2019). Nevertheless, these studies indicate that miR-330-5p plays multifaceted roles through modulating disparate downstream signaling. In this study, our results demonstrate miR-330-5p act in CRC as a tumor suppressor, which is largely in line with the role of miR-330-5p in cancers. Apart from that, we found that the downregulation of MAPK1 caused by circ_0071803 inhibition was rescued by either inhibiting miR-330-5p or overexpressing MAPK1 (Fig. 4). miR-330-5p inhibition and MAPK1 overexpression reversed the inhibitory effect of circ_0071803 knockdown in the growth and metastasis of CRC cells. Altogether, our mechanistic studies indicate that circ_0071803 enhances the MAPK signaling by sponging miR-330-5p, thereby promoting CRC progression.

In sum, our study suggests that circ_0071803 acts as a novel oncogene and the circ_0071803/miR-330-5p/MAPK1 axis is required for tumorigenesis in CRC. As such, circ_0071803 may be a potential therapeutic target for CRC treatment.

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Ethics approval and consent to participate. This study was approved by the institutional review board of the First Hospital of Jiaxing, and written informed consent was obtained from all participants.

Consent for publication. All patients provided their consent for publication.

Authors' contributions. Liyong Huang and Jiayi Wang designed this study; Liyong Huang and Guangjian Dou carried out all of experiments; Jiajun Lu performed cell culture and Western blot; Liyong Huang and Zhiheng Chen analyzed the data and prepared the first draft of this manuscript; Jiayi Wang approved the design of this work and revised this manuscript critically. All authors have read and approved the final manuscript.

Availability of data and materials. The datasets and raw materials are available from the corresponding author on reasonable request.

Competing interests. The authors declare no competing interests.

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