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Original Article

UBE2J2-mediated ubiquitination modification of MCM6 regulates proliferation and migration of cervical cancer cells

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Abstract: Microchromosome maintenance protein 6 (MCM6), a member of the MCM family, is involved in the regulation of various cancer progression. However, the role and related regulatory mechanisms in cervical cancer are unclear. The aim of this study was to investigate the role of MCM6 in cervical cancer and the regulation of MCM6 protein homeostasis by the ubiquitin-conjugating enzyme E2J2 (UBE2J2). To investigate the expression and function of MCM6 in cervical cancer, we used RT-qPCR and Western blot and found that MCM6 was upregulated. Cell function experiments indicate that MCM6 promotes the proliferation and migration of cervical cancer cells. The GEPIA database identified co-expressed genes with MCM6, and KEGG enrichment analysis showed that MCM6 was significantly associated with UBE2J2. We performed molecular docking of proteins and identified amino acid residues involved in the MCM6-UBE2J2 interaction. Using co-immunoprecipitation and Immunofluorescence experiments, we found that MCM6 binds to UBE2J2 and localizes to the nucleus. Ubiquitination experiments demonstrated that UBE2J2 mediates MCM6 ubiquitination. Response experiments showing that UBE2J2-mediated MCM6 ubiquitination modification regulates the proliferation and migration of cervical cancer cells. Our results suggest that the UBE2J2-MCM6 axis plays an important role in regulating cervical cancer proliferation and migration and is a promising therapeutic target for its treatment.

Keywords: Cervical cancer (CC), MCM6, UBE2J2, ubiquitination

Introduction

Globally, cervical cancer (CC) is one of the common malignant tumors of the female reproductive system, with about 500,000 new cases and 270,000 deaths each year [1, 2]. Clinical treatment is mainly based on surgery or radiotherapy, which can prolong the survival time of patients to a certain extent, but there is a lack of satisfactory and effective treatment options for patients with recurrent and metastatic cervical cancer [3, 4]. With the development of molecular biology, molecular studies exploring the pathogenesis of cervical cancer have been prompted to provide new insights for effective cervical cancer treatment [5-7].

Microchromosome maintenance protein 6 (MCM6) is a member of the MCM family, which plays an important role in DNA replication, cell cycle regulation, and tumorigenesis [8, 9]. Aberrant expression of MCM6 increases replication pressure, triggers genomic instability, and thus promotes carcinogenesis [10, 11]. MCM6 has been reported to be upregulated in various tumors and to promote tumor growth and metastasis. For example, in hepatocellular carcinoma, MCM6 promotes epithelial-mesenchymal transition (EMT) and metastasis by upregulating MEK/ERK activity [12]. In gastric cancer, inhibition of MCM6 significantly reduced cell proliferation and suppressed tumor growth in vivo [9]. However, little is known

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about the functional role of MCM6 in cervical cancer.

Ubiquitination, an important post-translational modification of proteins, profoundly affects the initiation, progression, and stress response of DNA replication by dynamically regulating the stability, localization, and function of key replication proteins [13-16]. In hepatocellular carcinoma (HCC), the E3 ubiquitin ligase RNF125 regulates the stability of MCM6 through ubiquitination, promoting its degradation and thereby inhibiting the proliferation of hepatocellular carcinoma cells [17]. In addition, during DNA replication stress or damage, MCM6 may be phosphorylated by ATM/ATR kinase, which in turn recruits E3 ligases (e.g., CRL4 or APC/C), triggering ubiquitination-dependent degradation or functional inhibition and preventing aberrant replication. Ubiquitin-conjugating enzyme E2J2 (UBE2J2) belongs to the family of E2 ubiquitin-conjugating enzymes in the ubiquitin-proteasome system (UPS), and is able to participate in the ubiquitination modification of proteins to regulate the cell cycle, DNA repair, and tumorigenesis [18, 19].

In this study, MCM6, a gene differentially expressed in cervical cancer, was found by GEO2R. Through bioinformatics analysis, we identified the UBE2J2 protein with potential binding to MCM6. UBE2J2, as an E2 ubiquitin-conjugating enzyme, can interact with MCM6 to form a complex. We investigated the UBE2J2-MCM6 relationship in cervical cancer to provide a new direction for future cervical cancer treatment.

Materials and methods

Cell culture

Human cervical cancer cell lines Hela, Siha, Caski, ME180, HT3, and H8 were purchased from Procell (Wuhan, China). The cell lines Hela, Siha, Caski, and H8 were cultured in DMEM medium containing 10% fetal bovine serum, while the cell lines ME180 and HT3 were cultured in McCoy's 5A medium. All cell lines were incubated in an incubator containing 5% CO_2 at 37°C. All cell lines were authenticated prior to their culture and tested for mycoplasma contamination every 3 months.

Western blot assay

Proteins were extracted using lysis buffer containing protease inhibitors, and protein concentrations were determined using a bicinchoninic acid (BCA) protein assay kit (KeyGen Biotech) with reference to the reagent vendor. Protein lysates were separated using 15% SDS-PAGE and transferred to PVDF membranes (Roche) after blocking non-specific signals using 5% nonfat milk. The membrane was incubated with the corresponding primary antibody at 4°C overnight, washed three times after incubation, and incubated with the secondary antibody of the corresponding species for 1 h. Finally, the protein bands were detected using Pierce ECL Protein Blotting Substrate (Thermo Scientific). Use Image J software for grayscale value analysis (MCM6: Proteintech China, 13347-2-AP, WB: 1:4000); (GAPDH: Proteintech China, 60004-1-Ig, WB: 1:50000); (FLAG (DYKDDDDK): Proteintech China, 80010-1-RR, WB: 1:50000); (HA: Proteintech China, 51064-2-AP, WB: 1:5000).

RNA extraction and RT-qPCR

Total RNA was extracted from each set of samples using Trizol reagent, and the RNA concentration of each sample was determined. Total RNA from each sample was reverse-transcribed into cDNA using a reverse transcription kit. The polymerase chain reaction was performed using the SYBR Green dye method (Vazyme). The qPCR amplification conditions were as follows: an initial denaturation at 95°C for 10 min, followed by denaturation at 95°C for 15 s; annealing/extension at 60°C for 1 h; and a melting curve analysis at 95°C for 15 s and 60°C for 1 min for 40 cycles. GAPDH was used as the housekeeping gene, and gene expression was calculated using the 2-ΔΔCT method. MCM6 forward 5'-GAGGAACTGATTCGTCCTGAGA-3' and reverse 5'-CAAGGCCCGACACAGGTAAG-3'; GAPDH forward 5'-CAAGGCTGTGGGCAAGGTCATC-3' and reverse 5'-GTGTCGCTGTTGAAGTCAGAGGAG-3'.

Cell transfection

When the cell fusion reached 80%-90%, the cells were ready for passaging. Hela and Siha cells in logarithmic growth phase were digested

with 0.25% trypsin and centrifuged, draped in serum-free medium, and seeded back into petri dishes. When the cell fusion reaches 70%-80% on the second day, the medium in the dish is changed to serum-free medium. Plasmids were transfected into cervical cancer cells using Lipofectamine 8000 (Beyotime Biotechnology) according to the manufacturer's instructions. After 6-8 h, the cell status changed to medium with serum, after which the cells were collected for subsequent experiments. All plasmids were purchased from Tsingke (Beijing, China).

Cell counting kit-8 (CCK-8) assay

Cell proliferation and viability were assayed using the Cell Counting Kit-8 (CCK-8) (Beyotime Biotechnology) according to the manufacturer's instructions. Transfected cells were inoculated into 96-well plates, and CCK-8 solution was added at the indicated time points after seeding. After incubation at 37°C for 2 h, absorbance was measured at 450 nm using an enzyme marker (Thermo, China). Measurements were made continuously for 5 days, and values were recorded.

Transwell migration assay

Plasmids were transfected into Hela and Siha cells and cultured for two days. After two days, the digestion was centrifuged and resuspended in serum-free medium for cell counting. 4×10^4 cells were inoculated in the upper chamber of the 24-well plate chambers with about 200 μL. The lower chamber was added with 700 μL of medium containing 10% fetal bovine serum. After incubation for 24 h, the chambers were removed, fixed with 4% paraformaldehyde, and stained with 1% crystal violet. The migrated cells were imaged and enumerated under an inverted microscope (8 μm pore size; Corning).

Colony formation assay

The transfected cells were inoculated into 6-well plates at a density of 500 cells per well and cultured for 10-14 days. Cells were fixed with 4% paraformaldehyde and stained with 1% crystal violet for 20 min at room temperature, then photographed for analysis.

Wound healing assay

The Hela and Siha cells were inoculated into 6-well plates at a density of 5×10^5 cells/well to achieve 80% confluence the next day. Plasmids were transfected into the cells. Three replicate wells were set up by making a straight line scratch in the middle of a six-well plate using a 200 μl tip of the gun, three times in parallel for each well. At 24 h and 48 h, images were captured under an inverted microscope to assess cell migration.

Immunofluorescence (IF) staining

The plasmids were transfected into Hela and Siha cells, and after the cells were adhered to the wall, they were fixed with 4% paraformaldehyde. They were then permeabilized with 0.5% Triton X-100, followed by 5% BSA-containing solution for 30 min at room temperature. Incubate with primary antibody at 4°C overnight. Staining was performed using the corresponding secondary antibody. Staining was performed with DAPI (Beyotime Biotechnology), and the sections were finally blocked with an anti-fluorescent bursting agent. The sections were observed using a confocal microscope (Nikon AR 1+). (MCM6: Proteintech China, 13347-2-AP, IF: 1:100); (UBE2J2: Proteintech China, 17713-1-AP, IF: 1:100); (FITC: Proteintech China, SA00003-1, SA00003-2, IF: 1:100); (Cy3: Proteintech China, SA00009-2, IF: 1:100).

Co-immunoprecipitation

Whole cell lysates of stably expressed Hela and Siha cells were prepared using lysis buffer. COIP was performed using FLAG-tagged antibodies, and the immune complexes were captured with protein A/G agarose beads (Santa Cruz). The complexes were validated by Western blot.

Statistical analysis

Data are presented as the mean ± standard deviation (SD). For comparisons across multiple continuous time points within the same subjects, Repeated Measures ANOVA was employed, followed by Tukey's post hoc test to identify specific intergroup differences. For intergroup comparisons involving multiple inde-

pendent groups, one-way analysis of variance (ANOVA) was conducted, followed by Tukey's post hoc test. Two-group comparisons were assessed using the two-tailed Student's t-test. Data processing and statistical analysis were performed using GraphPad Prism 8 and ImageJ software. In all cases, $P < 0.05$ was considered statistically significant.

Results

Bioinformatics analysis of MCM6 expression in cervical cancer

We analyzed MCM6 expression in cervical cancer tissues using the Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) (UALCAN, https://ualcan.path.uab.edu/index.html) (GEO: GSE9750, https:/ww.ncbinlm.nih.gov). The results showed that MCM6 expression was significantly upregulated in cervical cancer compared with normal cervical epithelial tissues (**Figure 1A-C**). The Human Protein Atlas (HPA, https://www.proteinatlas.org/) analyzed the expression levels of MCM6 in cervical cancer tissues and their corresponding normal tissues. The results showed that MCM6 protein expression was moderate and positive in cervical cancer tissues and almost absent in adjacent normal tissues (**Figure 1D**). The correlation between MCM6 and cervical cancer stage was analyzed using the UALCAN database. The results showed that the MCM6 gene expression level was significantly elevated in tumor stages I-IV compared with normal cervical epithelial tissues (**Figure 1E**). Analysis of MCM6 expression in normal, precancerous, and cancerous tissues using the GEO (GSE63514) dataset revealed significantly elevated MCM6 gene expression levels in precancerous and tumor tissues (**Figure 1F**). These results suggest that MCM6 is highly expressed in cervical cancer and may be involved in cervical cancer progression.

MCM6 expression is up-regulated in CC cells and promotes CC cell proliferation and migration

We used western blot and RT-qPCR to detect MCM6 protein and mRNA expression in five CC cell lines and normal cervical epithelial cells (H8). The results showed that the mRNA and protein levels of MCM6 were significantly increased in CC cells compared with normal cervical epithelial cells (H8) (**Figure 2A**, **2B**). CCK-8, colony formation, transwell migration, and wound-healing assays were next used to assess the effect of MCM6 on the proliferation and migration of CC cells (Hela and Siha). The experimental results showed a significant increase in cell proliferation and migration after MCM6 overexpression, indicating that MCM6 promoted proliferation and migration in the CC cell lines Hela and Siha. These experimental results suggest that MCM6 expression is upregulated in CC and can promote the proliferation and migration of CC cells (Hela and SiHa) (**Figure 2C-F**).

MCM6 binds UBE2J2 protein

We utilized GEPIA for data mining and screened the top 200 genes co-expressed with MCM6 in cervical cancer. KEGG analysis of these co-expressed genes was performed using the DAVID database (https://davidbioinformatics.nih.gov) (**Figure 3A**). The results showed that MCM6 was significantly associated with E2 ubiquitin conjugating enzyme (UBE2J2) (**Figure 3B**). We analyzed the 3D structure of MCM6 and downloaded the optimal model using the UniProt online platform (https://www.uniprot.org). Protein-protein docking of MCM6-UBE2J2 was performed by ZDOCK and MOE to model protein docking to obtain information about interacting amino acid residues (MCM6: green, UBE2J2: blue) (**Figure 3C**). The interaction between MCM6 and UBE2J2 was confirmed in Hela cells using CoIP experiments (**Figure 3D**). Immunofluorescence experiments demonstrated the co-localization of MCM6 and UBE2J2 in the nucleus (**Figure 3E**). To explore the correlation between MCM6 and UBE2J2, RT-qPCR detection of MCM6 mRNA after overexpression of UBE2J2 in Hela and Siha revealed that there was no difference in expression levels (**Figure 3F**). The abundance of MCM6 mRNA remained unchanged due to the stability of the transcriptional regulatory mechanism and the negative intracellular feedback mechanism. Next, western blot analysis showed that MCM6 protein expression was downregulated following UBE2J2 overexpression, and that UBE2J2 promoted MCM6 protein degradation. The experimental results showed that MCM6 protein expression was negatively correlated with UBE2J2 protein expression (**Figure 3G**).

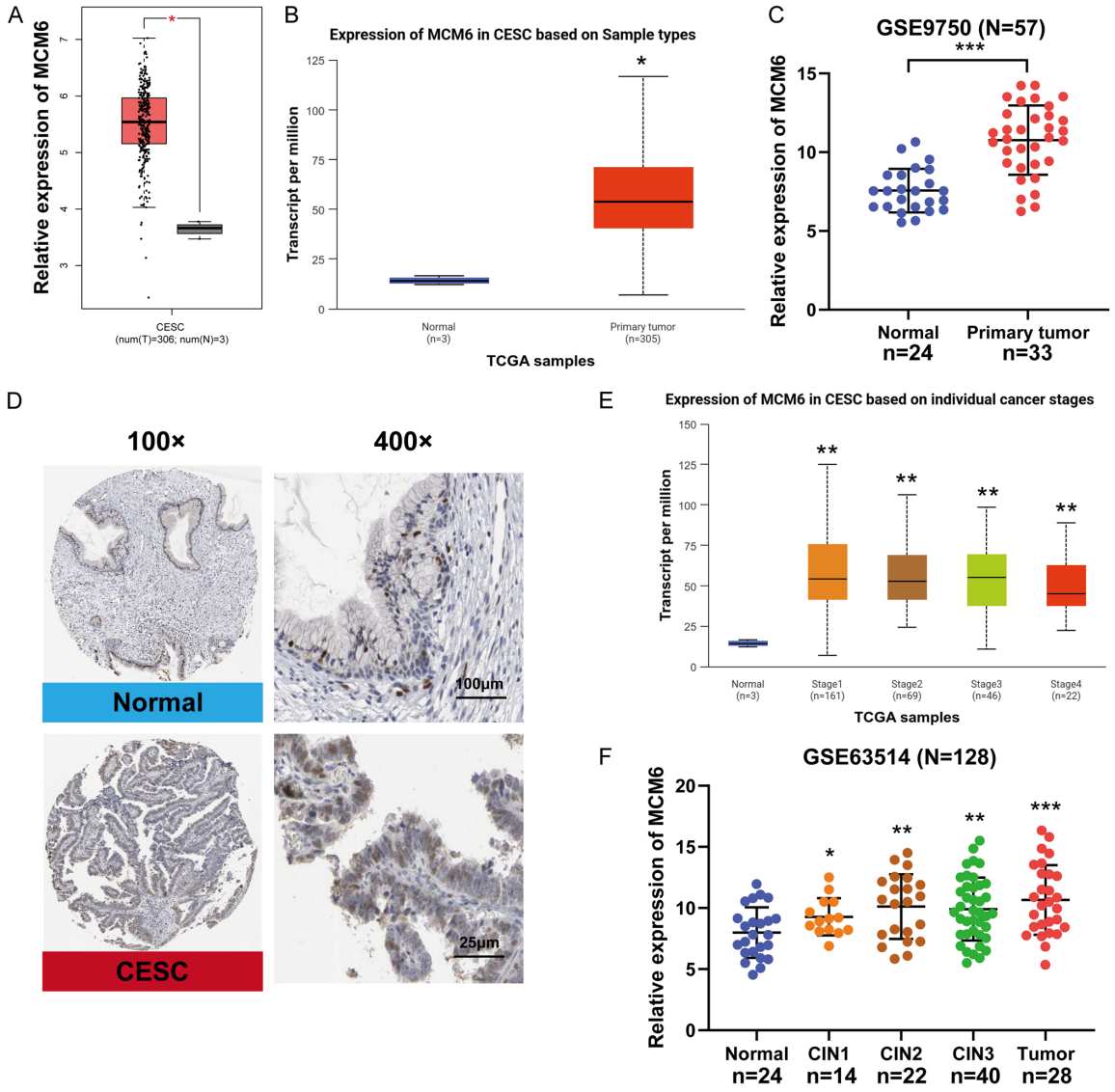

Figure 1. Bioinformatics analysis of MCM6 expression in cervical cancer. A. GEPIA database showing the expression of MCM6 in cervical cancer. B. UALCAN proteomics database showing MCM6 protein expression. C. GEO (GSE9750) dataset showing MCM6 expression in normal cervical tissue and cervical cancer tissue. D. HPA database showing MCM6 expression in cervical cancer tissues. E. UALCAN database showing the correlation between MCM6 and cervical cancer stage. F. GEO (GSE63514) dataset showing MCM6 expression in normal tissue, precancerous tissue, and cancerous tissue. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

The above results indicate that MCM6 binds UBE2J2 and is negatively correlated with it.

UBE2J2 inhibits the proliferation and migration of CC cells

To investigate the effects of UBE2J2 on CC cell lines, CCK-8, colony formation, transwell migration, and wound-healing assays were used to evaluate UBE2J2's effects on the proliferation and migration of Hela and Siha cells.

The results showed that both cell proliferation and migration were significantly reduced after UBE2J2 overexpression, indicating that UBE2J2 inhibited the proliferation and migration of CC cell lines Hela and Siha (**Figure 4A-D**).

UBE2J2 promotes ubiquitination and degradation of MCM6

Because MCM6 binds UBE2J2, a ubiquitin-binding enzyme that recognizes and acts on a

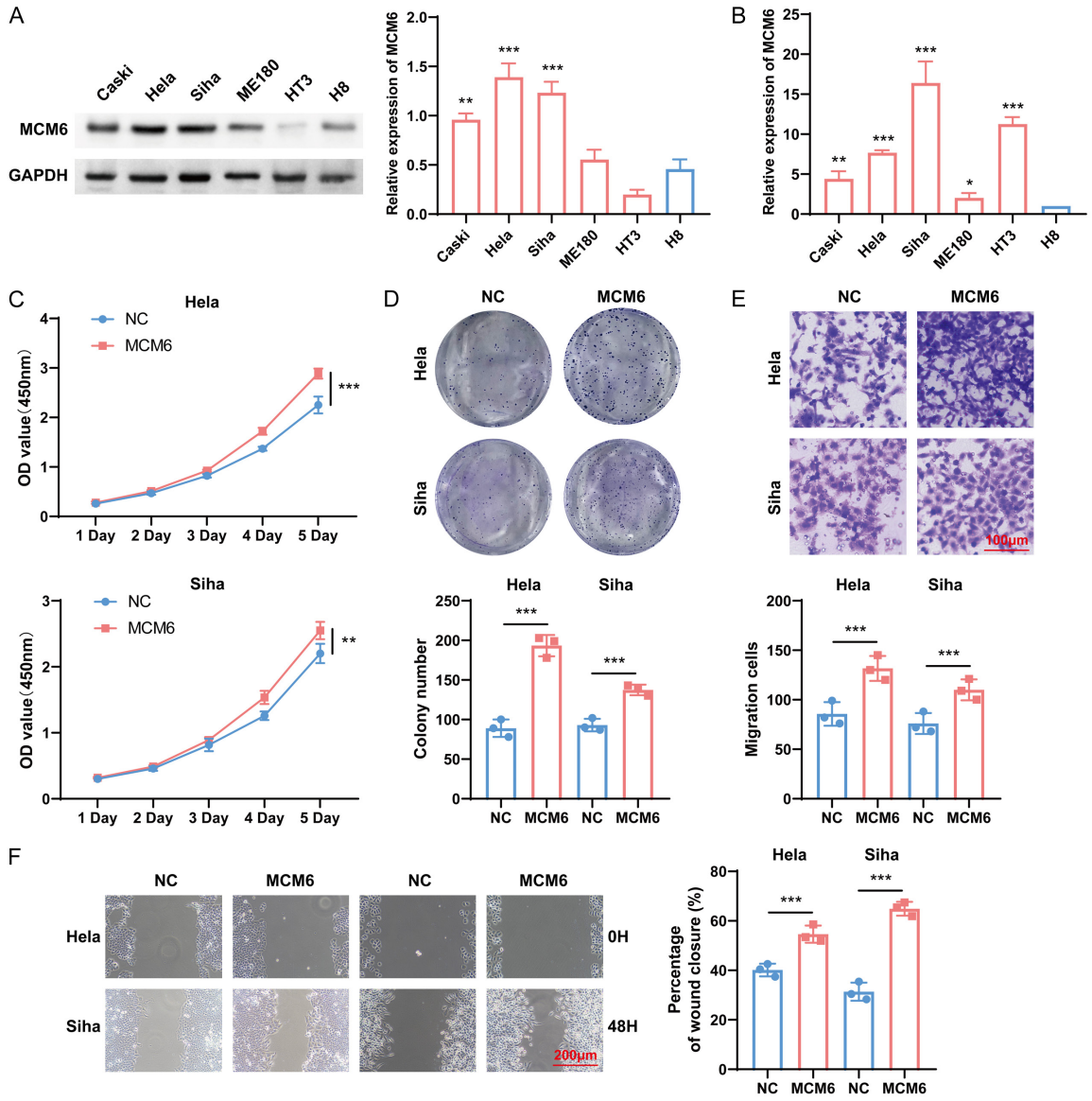

Figure 2. MCM6 expression is upregulated in cervical cancer cells and promotes the proliferation and migration of cervical cancer cells. A. Western blot was used to detect the protein expression of MCM6 in cervical cancer cell lines and normal cervical epithelial cells H8. B. The mRNA expression of MCM6 in cervical cancer cell lines and normal cervical epithelial cells (H8) was detected by RT-qPCR. C-F. The image was performed using the CCK-8, colony formation, transwell migration, and wound-healing assays to evaluate the effect of MCM6 on the proliferation and migration of cervical cancer cell lines Hela and Siha, and the results were statistically analyzed. n = 3 per group. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

variety of target proteins, it was next evaluated whether UBE2J2 affects MCM6 stability. After treatment with the proteasome inhibitor MG132, western blot results showed a significant increase in MCM6 protein levels in Hela and Siha (**Figure 5A**). In addition, Hela and Siha cells overexpressing UBE2J2 were treated with the protein synthesis inhibitor cycloheximide (CHX) for different times. Western blot analysis showed that MCM6 protein levels were significantly lower in the UBE2J2 group than in the control group (**Figure 5B**). Next, we added MG132 to prevent proteasomal degradation, and MCM6 and UBE2J2 to observe whether MCM6 affected UBE2J2 ubiquitination. CoIP results showed that the ubiquitination level of MCM6 was significantly increased upon UBE2J2 overexpression in Hela and Siha cells

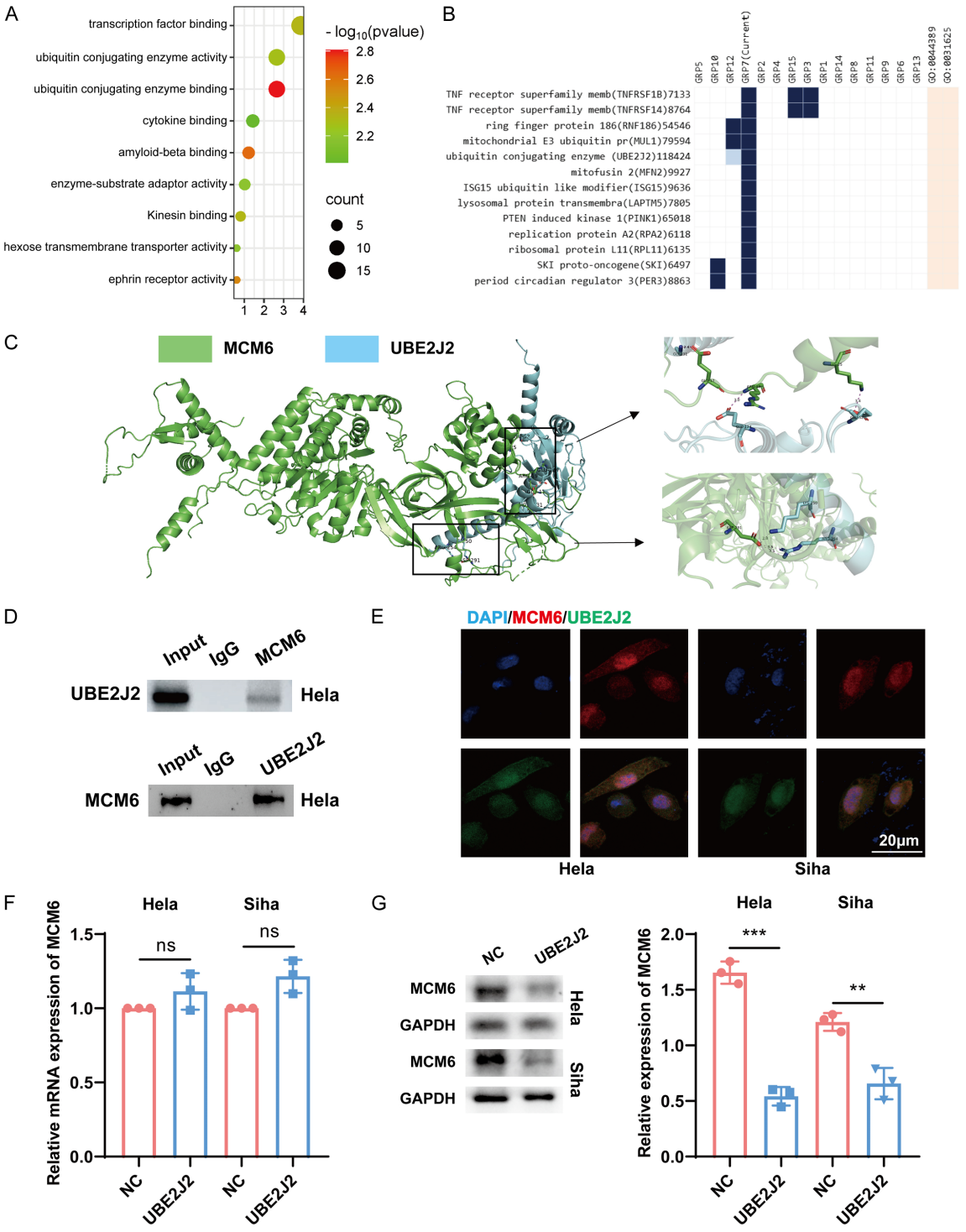

Figure 3. MCM6 protein binding to UBE2J2 protein. A. KEGG analysis of the enrichment pathway between MCM6 and its co-expressed genes in cervical cancer. B. Correlation between MCM6 and its co-expressed genes. C. Establishment of protein molecular docking model. D. Verification of the interaction relationship between MCM6 and UBE2J2 protein in cervical cancer by Co-immunoprecipitation. E. Immunofluorescence assay to verify the co-localized expression of MCM6 and UBE2J2 protein. F. RT-qPCR assay to verify the correlated expression between MCM6 and UBE2J2 mRNA. G. Western blot to verify the correlation between MCM6 and UBE2J2 protein. $^{**}P < 0.01$, $^{***}P < 0.001$.

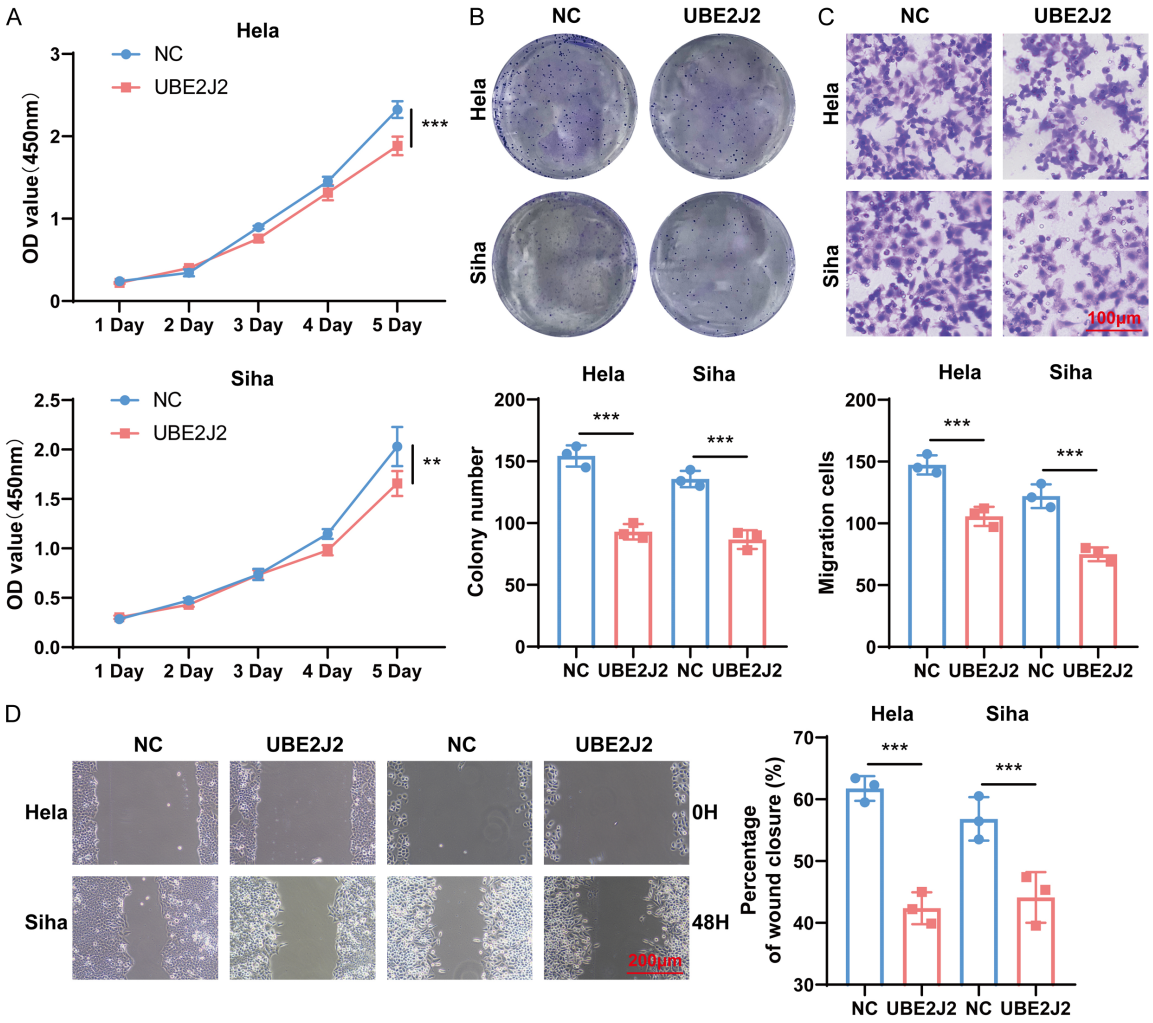

Figure 4. UBE2J2 inhibits the proliferation and migration of cervical cancer cells. A-D. The effects of the UBE2J2 protein on the proliferation and migration of cervical cancer cell lines Hela and Siha were evaluated and statistically analyzed using CCK-8, colony formation, transwell migration, and wound-healing assays. $^{**}P < 0.01$, $^{***}P < 0.001$.

(**Figure 5C**). Therefore, the above experimental results suggest that ubiquitination of MCM6 is mediated by UBE2J2.

UBE2J2 ubiquitination of MCM6 regulates CC cell proliferation and migration

To examine the effect of UBE2J2 ubiquitinated MCM6 on the proliferation and migration ability of CC cells, UBE2J2 was overexpressed on top of MCM6 in CC cells Hela and Siha. Western blot showed that protein expression was significantly reduced by overexpression of MCM6 followed by UBE2J2, compared with the overexpressed MCM6 group (**Figure 6A**). The effects of UBE2J2 ubiquitination of MCM6 on the proliferation and migration of CC cells were assessed using CCK-8, colony formation, transwell migration, and wound-healing assays. The experimental results showed that overexpression of UBE2J2 significantly reversed the promotion of MCM6 on the proliferation and migration of CC cells in vitro (**Figure 6B-E**). These data suggest that UBE2J2 ubiquitinates MCM6, thereby regulating the proliferation and migration of cervical cancer cells.

Discussion

Cervical cancer is a common gynecological malignant tumor, and its morbidity and mortality rate ranks among the top gynecological malignant tumors, which seriously threaten women's life and health [20, 21]. As a member

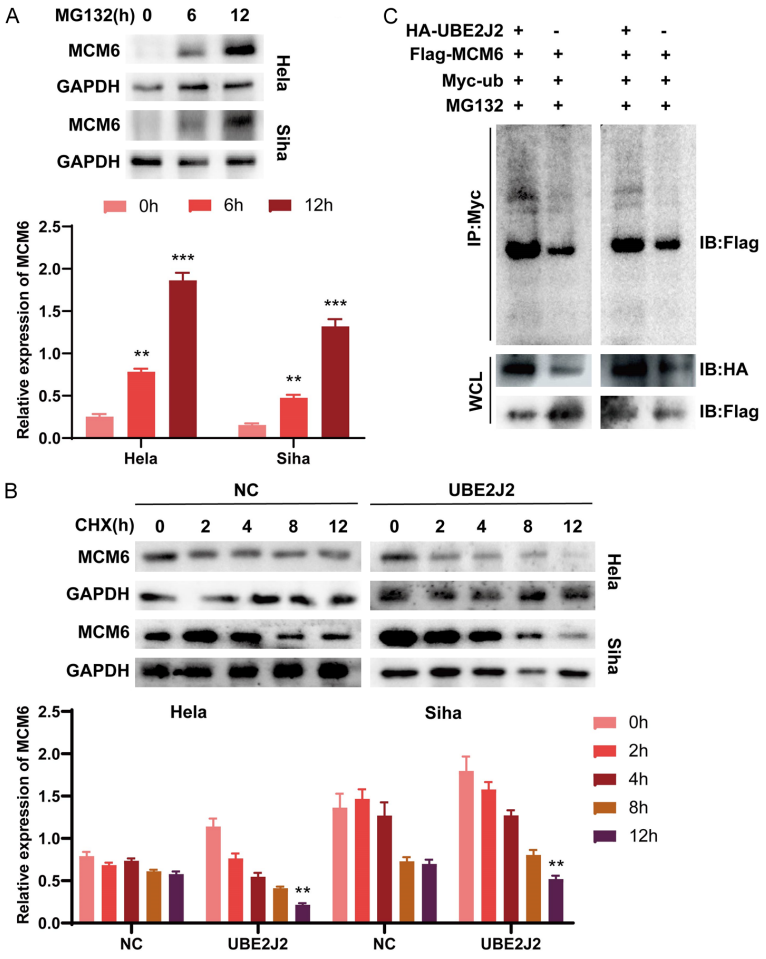

Figure 5. UBE2J2 promotes ubiquitination and degradation of MCM6. A. UBE2J2 regulation of MCM6 protein levels in Hela and Siha cells was verified using the proteasome inhibitor MG132 after treatment for different hours. B. Expression of protein in Hela and Siha cells pre-treated with CHX (50 μg/mL) for different hours was detected by western blot. C. Validation using Co-immunoprecipitation of UBE2J2 regulation of the ubiquitination level of MCM6. $^{**}P < 0.01$, $^{***}P < 0.001$.

of the MCM family, MCM6 plays a crucial role in the initiation and extension of DNA replication, a discovery of significant value for cervical cancer research [8]. Numerous studies have found that the expression of MCM6 is markedly elevated in a variety of cancer types, such as breast, lung, and colorectal cancers, and promotes tumor growth and metastasis [17, 22-27]. However, little is known about the role of MCM6 in cervical cancer.

In this study, the expression level of MCM6 in cervical cancer was analyzed using HPA, GEPIA, and UALCAN databases, and the results showed that MCM6 was highly expressed in cervical cancer. Cell function experiments showed that MCM6 promoted the proliferation and migration of the cervical cancer cell lines Hela and Siha. To further investigate the molecular mechanism of MCM6 in cervical cancer, we used the GEPIA database for data mining and identified the top 200 genes co-expressed with MCM6. Gene enrichment analysis was performed for these differential genes using the DAVID database. The results showed that MCM6 was significantly associated with ubiquitin-conjugating enzymes, and the E2 ubiquitin-conjugating enzyme UBE2J2, which showed the highest correlation with MCM6, was selected for subsequent studies.

The Ubiquitin-Proteasome Pathway (UPP) is one of the main mechanisms for the selective degradation of intracellular proteins, involved in key processes such as cell cycle regulation, stress response, and DNA repair through ubiquitin tagging of target proteins and their degradation by the proteasome [28-30]. UBE2J2 is a ubiquitin-conjugating enzyme that can recognize and act on a wide range of target proteins with broad substrate specificity, and is involved in ubiquitination modification of many important proteins in the cell, including proteins that are related to cell cycle regulation, DNA damage repair, and transcriptional regulation [18, 31]. To verify the interrelationship between MCM6 and UBE2J2, protein-protein docking was performed using a molecular docking model to identify interacting amino acid residues. MCM6 was shown to interact with UBE2J2 by Co-IP experiments. Subsequently, immunofluorescence experiments showed that MCM6 and UBE2J2 co-localized in the nucleus. In addition, there was no difference in RNA levels between UBE2J2 and MCM6, as analyzed by Western blot and RT-qPCR, and UBE2J2 protein expres-

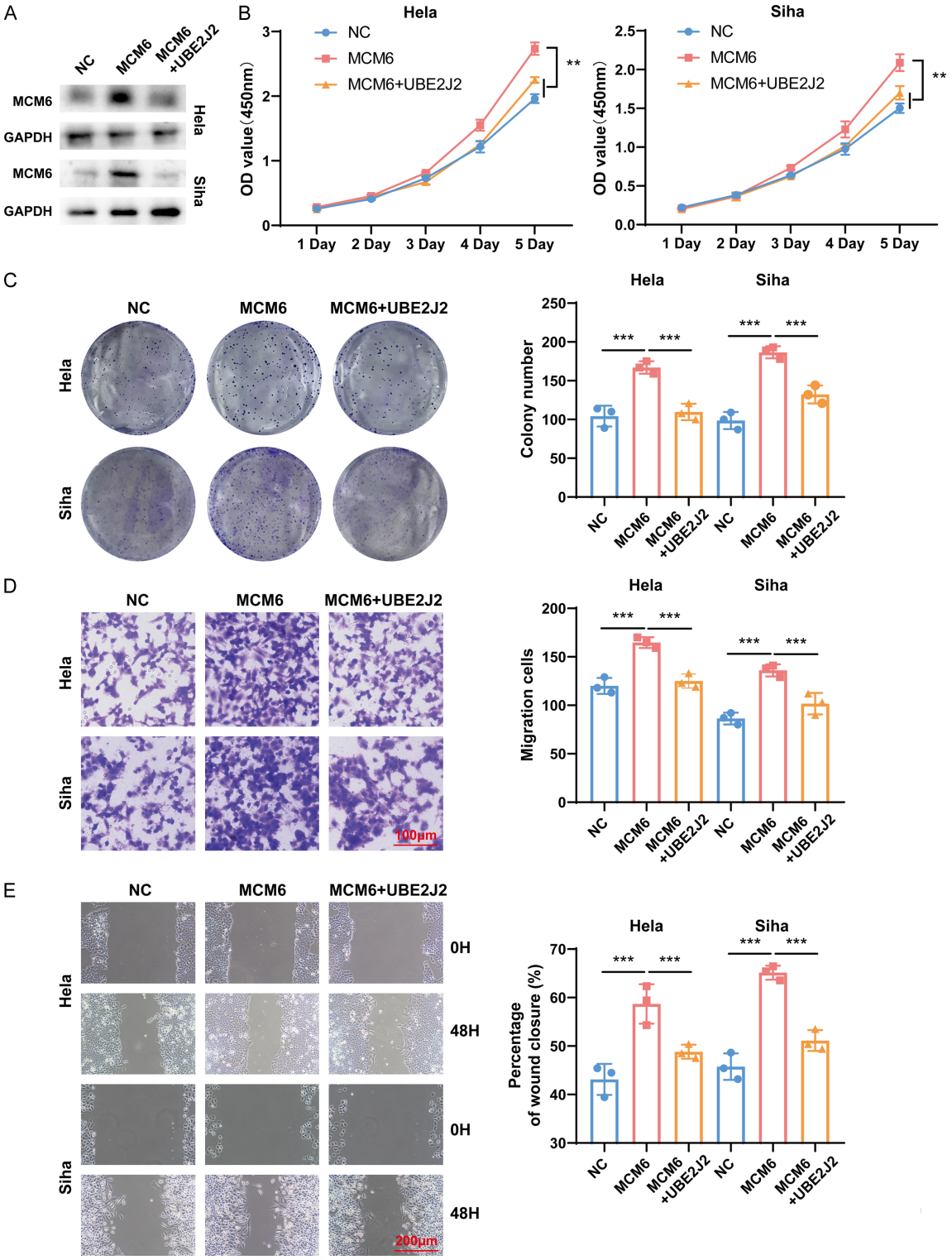

Figure 6. UBE2J2 ubiquitination of MCM6 can regulate the proliferation and migration of cervical cancer cells. A. Overexpression of UBE2J2 on top of overexpression of MCM6, and a western blot to detect MCM6 expression. B-E. Overexpression of UBE2J2 in cervical cancer, on top of MCM6 overexpression, was verified by CCK-8, colony formation, transwell migration, and wound-healing assays, which were validated and statistically analyzed. $^{**}P < 0.01$, $^{***}P < 0.001$.

sion was negatively correlated with MCM6 protein expression. To investigate whether UBE2J2 affects MCM6 stability, Co-IP experiments showed that UBE2J2 can regulate MCM6 ubiquitination, acting as a novel substrate for UBE2J2. Cell function experiments were performed to analyze the regulation of MCM6 by UBE2J2 in cervical cancer. The results showed that overexpression of UBE2J2 reversed the carcinogenic effect of MCM6 in cervical cancer cells Hela and Siha. Additionally, we will consider constructing genetically modified mouse models (such as conditional knockout or overexpression models) to explore the physiological and pathological roles of UBE2J2 and MCM6 in the development and progression of cervical cancer under conditions closer to physiological states.

In summary, the results showed that MCM6 was highly expressed in cervical cancer and could promote the proliferation and migration of cervical cancer cells. UBE2J2 could inhibit the proliferation and migration of cervical cancer cells, and the upregulation of UBE2J2 increased the ubiquitylation level of MCM6, which reversed the carcinogenic effect of MCM6 on cervical cancer cells Hela and Siha. Thus, ubiquitination of MCM6 by UBE2J2 can regulate the proliferation and migration of cervical cancer cells Hela and Siha, providing a promising direction for the clinical treatment of cervical cancer.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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