Abstract. Eukaryotic initiation factor 3 subunit M (EIF3M) is required for key steps in the initiation of protein synthesis, and dysregulation of EIF3M is associated with tumorigenesis. This study aimed to explore the clinicopathological and prognostic role of EIF3M in patients with colon adenocarcinoma. A total of 82 pathology specimens, 20 freeze-thawed tumors and 80 healthy controls were used to investigate the expression of EIF3M in colon adenocarcinoma through immunohistochemistry, western blotting, RT-qPCR and ELISA. In addition, Kaplan-Meier curves and Cox regression analysis were used to analyze overall survival (OS) and disease-free survival (DFS). Furthermore, the Oncomine database was used for analyzing EIF3M expression. The positive rate of EIF3M in colon adenocarcinoma was higher compared with that in normal colon tissues (62.20% vs. 29.27%; P<0.001). The mean score of EIF3M was also higher in colon adenocarcinoma compared with normal colon tissue (17.28±10.05 vs. 6.53±4.87; P<0.001). The levels of EIF3M expression in freeze-thawed tumors and serum from 20 patients with colon adenocarcinoma were higher than those in normal tissues and serum from healthy controls, respectively (P<0.001). Positive expression of EIF3M was associated with tumor size (P=0.002) and Dukes' stage (P<0.001). In multivariate Cox regression analysis, EIF3M expression was an independent prognostic factor for OS (P=0.003) and DFS (P=0.001). Oncomine database analysis showed a higher expression of EIF3M expression in colon adenocarcinoma compared with normal colon tissues, colon squamous cell carcinomas or gastrointestinal stromal tumors. In conclusion, EIF3M expression was associated with tumor size and Dukes' stage in colon adenocarcinoma. Hence, EIF3M is a potential prognostic indicator for colon adenocarcinoma.

Introduction

Colon cancer is one of the leading causes of cancer-associated mortality worldwide, with >800,000 recorded cases in 2018, for which radical surgery is the standard treatment (1). The prognosis of patients with colon cancer remains poor primarily due to recurrence (2). Upregulation of the expression of oncogenes is an important contributor to the etiology of cancer, and can promote abnormal proliferation and cell cycle progression (3). Hence, it is imperative to develop novel and reliable prognostic markers for patients with colon adenocarcinoma.

The eukaryotic initiation factor 3 (EIF3) is a complex translation initiation factor composed of 13 subunits (EIF3A to EIF3M) that is involved in mRNA modulation (4). The EIF3 complex is required for key steps in the initiation of protein synthesis (5). Dysregulated EIF3 subunits have been implicated in neurodegenerative disorders (such as Parkinson's disease), infection and tumorigenesis (6). Previous studies have demonstrated that EIF3 subunits regulate the AMP-activated protein kinase α (AMPKα), AKT/PI3K/mTOR and stress-activated kinase/JNK signaling pathways and the BCL-2 family of proteins, and play an important role in the development and growth of colon neoplasms (7,8). EIF3M encodes a protein of 42.5 kDa that is necessary for maintaining the structural integrity and translation initiation function of EIF3, and is also crucial for mouse embryonic development (9). EIF3M is upregulated in colon cancer and involved in the regulation of tumorigenesis-related genes, including migration inhibitory factor (MIF) and metallothionein 2 (MT2) (10,11). Silencing EIF3M expression leads to apoptosis of the HCT-116 colon cancer cell line (11). A previous study demonstrated that zinc
family member 1 (ZIC1) was upregulated in liposarcoma, and knockdown of ZIC1 in liposarcoma cell lines was associated with the degradation of EIF3M (12). Hence, EIF3M may be a pro-survival downstream target of ZIC1. These studies suggest that EIF3M expression is essential for carcinogenesis and could be used to develop a novel therapy for various cancer types.

Due to no studies reporting its prognostic role in the colon carcinoma, the present research investigated EIF3M expression in colon cancer by using a variety of laboratory techniques in conjunction with the Oncomine database, and its clinicopathological and prognostic value in patients with colon adenocarcinoma was explored.

**Materials and methods**

*Tissue samples.* This study was approved by the Kunshan First People’s Hospital Ethics Committee (Kunshan, China) and written informed consent was obtained from all the patients. The clinical and pathological data of 82 patients with colon adenocarcinoma (ratio male:female, 0.78:1) who had not received any radiotherapy or chemotherapy before surgery were reviewed. All cases were diagnosed with adenocarcinoma of the colon and underwent radical surgery at Kunshan First People’s Hospital between January 2010 and December 2012. Patients were diagnosed with Duke’s stage B or C disease, and received 8 courses of XELOX regimen (oxaliplatin combined with capecitabine; 130 mg/m² oxaliplatin IV on the first day and 2,000 mg/m²/day capecitabine for two weeks) (13). The mean age of the patients was 55.69±12.54 years, and the follow-up duration ranged from 3-60 months. The serum of the colon and underwent radical surgery at Kunshan First People’s Hospital between January 2010 and December 2012. Patients were diagnosed with Duke’s stage B or C disease, and received 8 courses of XELOX regimen (oxaliplatin combined with capecitabine; 130 mg/m² oxaliplatin IV on the first day and 2,000 mg/m²/day capecitabine for two weeks) (13). The mean age of the patients was 55.69±12.54 years, and the follow-up duration ranged from 3-60 months. The serum of 20 pairs of fresh-frozen colon tumors and matched normal tissues (>5.0 cm from tumor tissues) obtained from patients with colon adenocarcinoma was explored with ELISAs. Additionally, 20 pairs of fresh-frozen colon tumors and matched normal tissues (>5.0 cm from tumor tissues) obtained from patients with colon adenocarcinoma were collected for total protein and mRNA extraction. The levels of CEA, CA19-9 and CA12-5 were investigated by ELISA in the laboratory department of Kunshan First People’s Hospital (Kunshan, China) when patients were hospitalized.

**Immunohistochemistry (IHC) and evaluation of immuno-histochemical staining.** Tissues were fixed in 10% formalin at 20°C for 8 h and then embedded in paraffin blocks. 5-μm paraffin-embedded sections were used for EIF3M immunohistochemical staining with an SP Rabbit and Mouse HRP kit (cat. no. CW2069M, CoWin Biosciences). Endogenous peroxi-dase enzymes blocking buffer was used at 20°C for 10 min. These two blocking reagents were constituent parts of this kit. The primary antibody, EIF3M rabbit polyclonal antibody (cat. no. bs-9033R, BIOSS), was diluted at 1:100 in phosphate-buffered saline (PBS). PBS without primary antibodies was used as a negative control. The SP Rabbit and Mouse HRP kit (cat. no. CW2069M, CoWin Biosciences) was used to conduct a secondary incubation at 20°C for 10 min, according to the manufacturer’s protocol. Two pathologists independently evaluated the immunoreactivity scores (IRS) for EIF3M expression through a semi-quantitative assessment system. Slides were photographed using an inverted light microscope (magnification, x400; Nikon Corporation). The IRS values were a combination of a score for the staining intensity and a score of the percentage of cells. The staining intensity was defined as: 0, no staining; 1, mild staining; 2, moderate staining; and 3, strong staining. The scores for the percentage of cells were defined as: '0-100% = 0, 0%; 1, 1-10%; 2, 11-20%; 3, 21-30%; 4, 31-40%; 5, 41-50%; 6, 51-60%; 7, 61-70%; 8, 71-80%; 9, 81-90%; and 10, 91-100%'). The total IRS was calculated by multiplying the staining intensity score by the staining percentage score, and ranged from 0 to 30. Any disagreement was resolved by discussion. EIF3M expression was considered positive only when IRS >10.

**Western blotting.** A total of 20 pairs of fresh-frozen specimens were used for western blotting. Total protein of each tissue was extracted using RIPA lysis buffer (Beyotime Institute of Biotechnology) containing protease inhibitor cocktail (Pierce; Thermo Fisher Scientific, Inc.). The supernatants were collected and their protein concentration was measured using a BCA protein assay kit (Pierce; Thermo Fisher Scientific, Inc.), 20 μg of each sample was loaded per lane on 8-16% gels (Beyotime Institute of Biotechnology) and proteins were separated by SDS-PAGE (EMD Millpore). Proteins were transferred to PVDF membranes (Beyotime Institute of Biotechnology). Membranes were blocked in 5% non-fat dry milk with TBST for 1 h at room temperature. EIF3M rabbit polyclonal antibody (1:500; BIOSS) and β-actin mouse monoclonal antibody (cat. no. AF0003; 1:1,000; Beyotime Institute of Biotechnology) were used to incubate membranes at 4°C overnight. Secondary antibodies (1:1,000; anti-rabbit, cat. no. A0208; and anti-mouse, cat. no. A0216; both Beyotime Institute of Biotechnology) were used to conduct a secondary incubation at 20°C for 10 min, and detected using an Enhanced Chemiluminescence Detection system (Beyotime Institute of Biotechnology). The relative densities were quantified with a digital imaging analyzer, ImageJ version 1.4.1 (National Institutes of Health). EIF3M expression was normalized to β-actin.

**RT-qPCR.** TRIzol reagent (Thermo Fisher Scientific, Inc.) was used to isolate the total RNA from each tissue, and 2 μg RNA was reverse transcribed using the SuperScript II RNase-Reverse Transcriptase system (Invitrogen; Thermo Fisher Scientific, Inc.) at 50°C for 15 min, and then 85°C for 2 min. qPCR was performed using an iQ5 real-time PCR detection system (Bio-Rad Laboratories, Inc.) with the SYBR Green Premix Ex Taq™ kit (Takara Bio, Inc.). The PCR cycling conditions were as follows: 94°C for 4 min, followed by 40 cycles of 95°C for 1 min, 60°C for 1 min and 72°C for 1 min. PCR primers were designed as follows: EIF3M forward, 5'-ATG TGT ATT GTA CGA GCA T-3' (198 bp); and reverse, 5'-TGT ATT GTA CGA GCA T-3' (198 bp); and β-actin forward, 5'-GGA AAT TCT GGG CTG TAC CTA AGG-3' and reverse, 5'-CAG GAA GGAG CTC GAA AGA GTG-3' (185 bp). The relative expression of EIF3M was expressed using the 2^ΔΔCq method, where ΔΔCq=(Cq_fibroblast-elF3M-Cq_fibroblast-β-actin)-(Cq_tumor-elF3M-Cq_tumor-β-actin) (14).

**ELISA.** The EIF3M ELISA kit (cat. no. S00143, Shanghai Yuanye Biotechnology Co., Ltd) was used to detect the levels...
of EIF3M in serum of 20 patients with colon adenocarcinoma patients and 80 healthy controls. Following the manufacturer’s instructions, the OD value for each sample was detected using a microplate reader (wavelength, 450 nm), and the level of EIF3M was calculated using a standard curve drawn using Excel 2016 (Microsoft Corporation).

Oncomine database analysis. The following 6 datasets were selected from the Oncomine database (https://www.oncomine.org/): Skrzypczak Colorectal (69 samples); Skrzypczak Colorectal 2 (15 samples); Graudens Colon (30 samples); Ki Colon (91 samples); TCGA Colorectal (123 samples) and Hong Colorectal (82 samples) (15-18). These datasets compare expression of EIF3M in colon or colorectal carcinoma with expression in normal tissues.

Statistical analysis. SPSS 20.0 (IBM Corp.) and GraphPad 6.0 (GraphPad Software, Inc.) were used for statistical analyses, and P<0.05 was considered to indicate a statistically significant difference. Pearson’s χ² test was used to analyze the association of EIF3M expression with clinicopathological characteristics. Continuous variables, expressed as the mean ± SD, were analyzed using a Student’s t-test; a paired t-test was used for comparing tumors with adjacent normal tissues, and an unpaired t-test was used for comparing the serum of patients with colon adenocarcinoma with that of the healthy controls. In addition, Cox univariate and multivariate regression analysis and Kaplan-Meier curves with log-rank test were also used to analyze overall survival (OS) and disease-free survival (DFS).

Results

Expression of EIF3M in colon adenocarcinoma. EIF3M was expressed in the cytoplasm in both colon adenocarcinoma and normal colon tissues (Fig. 1A and B). The positive rate of EIF3M in colon adenocarcinoma was higher than that in normal colon tissues (62.20 vs. 29.27%; P<0.001). The mean IRS of EIF3M in colon adenocarcinoma was significantly higher than that in normal colon tissues (17.28±10.05 vs. 6.53±4.87; P<0.001; Fig. 1C). The levels of EIF3M mRNA and protein in freeze-thawed tumors were higher than those in corresponding normal tissues (P<0.001; Fig. 1D-F). In addition, the average level of EIF3M in the serum supernatants of 20 patients with colon adenocarcinoma was significantly higher compared with that in 80 healthy controls (2625.3±986.4 vs. 1203.3±493.5 pg/ml; t=9.17; P<0.001).

Association between EIF3M and clinico-pathological parameters in colon adenocarcinoma. According to the IRS values, 51 patients were classed into the ‘positive group’ (IRS >10) and used for subsequent analysis. As presented in Table I, positive expression of EIF3M was associated with tumor size (P=0.002) and Dukes’ stage (P<0.001), whilst there was no association found between EIF3M expression and other parameters, including age, sex, location, differentiation, CEA, CA19-9 and CA12-5.

Association between EIF3M expression and OS. In the Kaplan-Meier analysis, the OS rate of the ‘positive group’ was significantly lower than the ‘negative group’ (P=0.006; Fig. 2A). Based on univariate Cox regression analysis, EIF3M, tumor size, differentiation, Dukes’ stage, serum CEA and serum CA12-5 were associated with OS (P<0.01; Table II). Based on multivariate analysis, EIF3M expression (P=0.003), differentiation (P<0.001), Dukes stage (P<0.001) and serum CEA (P<0.001) were independent prognostic factors for OS rate for patients with colon adenocarcinoma (Table III).

Association between EIF3M expression and DFS. The DFS rate of patients with positive expression of EIF3M was significantly lower than that of patients with negative expression (P=0.002;
Fig. 2B). Based on univariate Cox regression analysis, EIF3M, differentiation, Dukes’ stage, serum CEA and serum CA12-5 were all significantly associated with DFS (P<0.05; Table II). In multivariate Cox regression analysis, EIF3M expression (P=0.001), differentiation (P=0.009), Dukes’ stage (P=0.001) and serum CEA (P=0.011) were independent prognostic factors for DFS (Table III).

EIF3M expression in colon cancer using Oncomine. All 6 datasets from the Oncomine database showed a higher expression of EIF3M in colon/colorectal carcinoma tissues compared with normal tissues (P<0.001; Fig. 3A). The Ki Colon dataset also highlighted the top 15 genes related to{EIF3M by co-expression analysis (Fig. 3B). These genes were all expressed to significantly higher levels in colon adenocarcinoma compared with normal tissues, and exhibited a strong co-expression correlation (correlation index, 0.675-0.876).

Colon cancer is the third most common malignancy and has become a great public health concern (1). In order to explore novel and valuable biomarkers for colon cancer, the present study investigated EIF3M expression and evaluated its clinicopathological and prognostic roles in patients with colon cancer. EIF3M is one of the most pivotal subunits of the EIF3 complex and accelerates protein synthesis and ribosomal recycling (6). A previous study revealed the elevated expression of EIF3M and other core subunits is indispensable

### Table I. Association of EIF3M expression in patients with colon adenocarcinoma with clinicopathological variables.

| Variables | n   | Positive, n (%) | Negative, n (%) | χ² | P-value |
|-----------|-----|----------------|----------------|-----|---------|
| Total     | 82  | 51 (62.20)     | 31 (37.80)     |     |         |
| Age, years|     |                |                | 0.049 | 0.825  |
| ≤55       | 49  | 30 (61.29)     | 19 (38.71)     |     |         |
| >55       | 33  | 21 (61.18)     | 12 (38.71)     |     |         |
| Sex       |     |                |                | 0.032 | 0.858  |
| Male      | 36  | 22 (43.14)     | 14 (45.16)     |     |         |
| Female    | 46  | 29 (56.86)     | 17 (54.84)     |     |         |
| Tumor size, cm |    |                |                | 10.038 | 0.002 |
| ≤5        | 48  | 23 (45.10)     | 25 (80.65)     |     |         |
| >5        | 34  | 28 (54.90)     | 6 (19.35)      |     |         |
| Location  |     |                |                | 0.848 | 0.357  |
| Right colon | 37  | 21 (41.18)     | 16 (51.61)     |     |         |
| Left colon| 45  | 30 (58.82)     | 15 (48.39)     |     |         |
| Differentiation |   |                |                | 5.597 | 0.061  |
| I         | 13  | 7 (13.73)      | 6 (19.35)      |     |         |
| II        | 40  | 21 (41.18)     | 19 (61.30)     |     |         |
| III       | 29  | 23 (45.09)     | 6 (19.35)      |     |         |
| Dukes’ stage |      |                |                | 14.366 | <0.001 |
| B         | 47  | 21 (41.18)     | 26 (83.87)     |     |         |
| C         | 35  | 30 (58.82)     | 5 (16.13)      |     |         |
| Serum CEA, ng/ml |  |                |                | 3.319 | 0.068  |
| <5        | 32  | 16 (31.37)     | 16 (51.61)     |     |         |
| ≥5        | 50  | 35 (68.63)     | 15 (48.39)     |     |         |
| Serum CA19-9, U/ml | |                |                | 3.701 | 0.054  |
| <37       | 69  | 46 (69.0)      | 23 (74.19)     |     |         |
| ≥37       | 13  | 5 (9.0)        | 8 (25.81)      |     |         |
| Serum CA12-5, U/ml | |                |                | 2.146 | 0.120  |
| <35       | 55  | 31 (60.78)     | 24 (77.42)     |     |         |
| ≥35       | 27  | 20 (39.22)     | 7 (22.58)      |     |         |

EIF3M, eukaryotic initiation factor 3 subunit M; CEA, carcino-embryonic antigen; CA, carbohydrate antigen.
to carcinogenesis. Goh et al (11) reported that EIF3M was upregulated in colon cancer and colon cancer cell lines. After knocking down EIF3M expression in the HCT-116 colon cancer cell line, proliferation was reduced and the apoptosis reduction.
rate was promoted due to a prolonging of the sub-G0/G1 stage of the cell cycle (11). In concordance with previous studies, the current study proved that the expression of EIF3M in colon adenocarcinoma was significantly higher when compared with normal tissues. In addition, EIF3M expression was associated with tumor size and Dukes' stage. In Kaplan-Meier analysis and Cox regression analysis, the role of EIF3M in negatively influencing prognosis of patients with colon adenocarcinoma was confirmed. Therefore, positive EIF3M expression may indicate that patients with colon adenocarcinoma may be at a later Dukes' stage and have a worse prognosis.

Dukes' stage was first established in 1935, and is a traditional medical clinical classification, including stages A to D (13). Patients at stage A weren't treated with chemotherapy and patients at stage D had not received a radical resection. To more accurately assess the role of EIF3M in colon carcinoma, the current study only enrolled patients at stage B or C. Tumors at stage B invaded the serosa without any lymph node metastasis, whilst tumors at stage C invaded the serosa with lymph node metastasis. The influence of EIF3M expression on lymph node metastasis was not assessed separately. In this study, positive EIF3M expression was higher in colon adenocarcinoma patients at stage C than those at stage B. In addition, Dukes' stage was an independent factor of OS and DFS, which suggested that colon adenocarcinoma patients with positive EIF3M expression in tumors had a worse prognosis. Hence, further research is required to identify if EIF3M could be used as a therapeutic target for anticancer drugs. As serum levels of EIF3M could be found in the blood, further studies are needed to evaluate the role of EIF3M in monitoring of colon cancer.

A study by Goh et al (11) has demonstrated the molecular mechanism of EIF3M in colon cancer. MIF and MT2 expression was found to be downregulated when EIF3M was knocked down in the HCT-116 colon cancer cell line (11). MIF not only plays a critical role in inflammation and immunity by deregulating the inhibitory effect of glucocorticoids, but is also associated with tumorigenesis and tumor growth (19,20). MT2 is a member of the metallothionein family that performs a plethora of metal ion-related events in stress responses, tumorigenesis, neurodegeneration and inflammation (21). A previous study demonstrated that MT2 is involved in cell migration, proliferation and angiogenesis and could be a novel regulator of vascular endothelial growth factor C expression (22). In addition, EIF3M knockdown interfered with cell
cycle regulation and induced cell apoptosis by degradation of cell division cycle 25 homolog A (22).

It has been shown that other EIF3 subunits are also associated with colon cancer. EIF3A is overexpressed in colon tumors, and elevated EIF3A expression inhibits Caco-2 cell differentiation (23). EIF3B knockdown inhibits the proliferation and increases the apoptotic rate of SW1116 colon cancer cells (24). EIF3C gene knockdown suppresses the proliferation of RKO colon cancer cells; the cell cycle is arrested at G0/G1 stage and apoptosis is also induced (25). Knockdown of EIF3D inhibits proliferation of HCT116 colon cancer cells via modulating AMPKα, glycogen synthase kinase 3β and JNK (8). Knockdown of EIF3E reduces the proliferation and clonality of HCT116 cells and promotes cell apoptosis (26). In addition, high EIF3E expression might predict poor prognosis in colon cancer (26). Qi et al (27) demonstrated that EIF3I was a proto-oncogene in colon carcinoma, and worked by activating the β-catenin signaling pathway and upregulating cyclooxygenase 2. This body of research shows that translation initiation factors including EIF3A, EIF3B, EIF3C, EIF3D, EIF3E, EIF3I and EIF3M promote the formation of colon neoplasms. The present study demonstrated that EIF3M could be an indicator of poor prognosis in patients with colon adenocarcinoma. The prognostic role of all the subunits of the EIF3 complex should be investigated in the future. In conclusion, elevated EIF3M expression in patients with colon adenocarcinoma was associated with larger tumor size, Dukes' stage C, and worse OS and DFS rates. Therefore, upregulated EIF3M is a putative candidate biomarker for poor prognosis in colon adenocarcinoma patients.

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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 on reasonable request.

Table IV. Information and functions of the top 15 genes associated with EIF3M expression using the Ki Colon dataset.

| Genes | Chromosomal location | Ensembl version | Locus type | Functions |
|-------|----------------------|----------------|------------|-----------|
| IPO7  | 11p15.4              | ENSG00000205339| Gene with protein product | Ribosome biogenesis related proteins; carcinogenesis (28) |
| SULT4A1 | 22q13.31           | ENSG00000130540| Gene with protein product | Neuronal-associated genes; carcinogenesis (29) |
| GNE   | 9p13.3               | ENSG00000159921| Gene with protein product | GNE myopathy (30) |
| NOB1  | 16q22.1              | ENSG00000141101| Gene with protein product | Carcinogenesis in colorectal cancer (31) |
| EIF2S2| 20q11.22             | ENSG00000125977| Gene with protein product | Essential for cell proliferation; regulators of oncogenesis (32) |
| UBA2  | 19q13.11             | ENSG00000126261| Gene with protein product | Carcinogenesis (33) |
| ATIC  | 2q35                 | ENSG00000138363| Gene with protein product | Polymorphisms in cancer (34) |
| CCT6B | 17q12                | ENSG00000132141| Gene with protein product | Implicated in cancer (35) |
| CCT6P1| 7q11.21              | ENSG00000228409| Pseudogene | Associated with sickle cell disease (36) |
| DARS  | 2q21.3               | ENSG00000115866| Gene with protein product | Reinitiating DNA replication (37) |
| CCDC34| 11p14.1              | ENSG00000109881| Gene with protein product | Carcinogenesis in colorectal cancer (38) |
| RNASEH2B | 13q14.3             | ENSG00000136104| Gene with protein product | Its deletion related to cancer occurrence (39) |
| SNRPE | 1q32.1               | ENSG00000182004| Gene with protein product | Poor prognostic indicator (40) |
| CDK7  | 5q13.2               | ENSG00000134058| Gene with protein product | Transcriptional cyclin-dependent kinase; carcinogenesis (41) |
| SNRPB2| 20p12.1              | ENSG00000125870| Gene with protein product | mRNA splicing; carcinogenesis (42) |

EIF3M, eukaryotic initiation factor 3 subunit M.
Authors’ contributions

QHW, MZ and FL conceived and designed the study, QHW, MZ, MHZ and XY performed the experiments and wrote the manuscript. QHW, XJG and FC analyzed the data. All authors read and approved the manuscript and agreed to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The present study was approved by the Kunshan First People’s Hospital Ethics Committee (Kunshan, China) and written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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