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Original Article

LINC01420 is associated with clinical progression of colorectal carcinoma and facilitates cell proliferation via modulating cell cycle regulators

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Abstract: Colorectal carcinoma (CRC), is a main cause of cancer-related mortality worldwide, and it is a prevalent malignant tumor in humans. Of note, numerous patients with CRC are diagnosed in the advanced stages of CRC. The prognosis of survival in advanced CRC patients remains less than 50%. TCGA and GEPIA datasets were used to explore the expression level of LINC01420, and qRT-PCR was used to assess LINC01420 expression level in different human CRC cells. StarBase and miRanda were applied to predict the binding sites corresponding to respective lncRNA and miRNA. The potential functions of LINC01420 in CRC were assessed by Bioinformatics analysis. Moreover, we applied a loss-of-function assay to validate the roles of LINC01420 in CRC. Our data indicated that the expression level of LINC01420 was up-regulated in CRC tissues after being normalized to that in healthy tissues with The Cancer Genome Atlas (TCGA) database. Bioinformatics analysis showed LINC01420 was associated with the regulation of carbon metabolism and proliferation. A loss-of-function assay revealed knockdown of LINC01420 significantly suppressed cell proliferation, cell cycle, but induced cell apoptosis in CRC cells. Our study showed LINC01420 could be a new potential biomarker for CRC.

Keywords: Colorectal carcinoma, lncRNAs, biological function, molecular mechanism

Introduction

Colorectal carcinoma (CRC), a common type of malignant tumor in humans, is one of the pivotal reasons for mortality of cancer-related deaths all over the world [1]. Of note, a majority of the CRC patients are diagnosed in advanced stage CRC [2]. The survival prognosis of advanced CRC patients remains to be less than 50%. Therefore, there is a pressing urgency to identify newly produced indicators to asses the status of patients with CRC in diagnosis and prognosis.

It is estimated that more than 70% of the human genome is transcribed as non-coding RNA (ncRNA) [3]. ncRNAs is classified into small ncRNAs with no more than 200 nt and long ncRNAs (lncRNAs) with at least 200 nt [4]. Small ncRNAs, include microRNAs (miRNAs) and snoRNAs [5], which have been well known studied. Long noncoding RNAs (lncRNAs), of which transcripts possess at least 200 nucleotides and have scant potential of coding [6], are shown to be linked with human cancer progression, and its expression level presents highly cellular- and tissue-specificity [7]. In recent studies, emerging evidence shows lncRNAs participat in tumorigenesis and progression of CRC [8-10]. For instance, lncRNA-APC1 was found to be down-regulated in tumor samples and exhibits association with advanced clinical stages and poorly prognostic status of patients with CRC. Knockdown lncRNA-APC1 suppressed CRC growth and metastasis through Rab5b [11]. LncRNA SNHG5 was reported to promote CRC growth via STAU1-mediated mRNA destabilization [12]. LINC01420 is a novel lncRNA and was shown to have a relationship with human disease progress. A previous study showed that the rs5914778 *loci* within LINC01420 was associated with systemic lupus erythematosus (SLE) [13]. Recently, one study indicated the expression level of

LINC01420 was enhanced in nasopharyngeal carcinoma samples and induced tumor cell metastasis [14]. However, the functional roles of LINC01420 in CRC are not well understood.

Here, our results revealed that the LINC01420 expression level was up-regulated in CRC tissues when compared to that in normal tissues by analyzing the TCGA database. The functions of LINC01420 in CRC were predicted by bioinformatic analysis, and the roles of LINC01420 in CRC was further validated by loss-of-function experiments. Our study aimed to uncover the roles of LINC01420 in CRC, including biological functions, underlying mechanisms, and clinical profile.

Materials and methods

Public datasets analysis

LINC01420 expression level in either colon adenocarcinoma (COAD) and matched normal tissues or Rectum adenocarcinoma (READ) and matched normal tissues, were analyzed in GEPIA datasets (http://gepia.cancer-pku.cn/) based on TCGA database.

Cell lines

SW620 and SW480 were aquired from the American Type Culture Collection (ATCC, Manassas, VA, USA). Both of them were cultured in Dulbecco's modified Eagle's (Gibco, Gaithersburg, MD) with 10% FBS (HyClone, Logan, UT) and 1% penicillin/streptomycin at 37°C in an incubator containing 5% CO_2.

Quantitative Real-time PCR (qRT-PCR)

The RNA from human CRC tissues and cell lines was harvested using Trizol (Invitrogen, Carlsbad, CA, USA) and was reversely transcribed into cDNA by PrimeScript RT reagent kit (Takara Biotechnology, Dalian, China), followed by a qRT-PCR with the use of TB Green Premix Ex Taq II (Takara Biotechnology, Dalian, China) on ABI7500 Real-time PCR system (Applied Biosystems, Foster City, CA, USA). All primers used for LINC01420 are shown below: 5'-CACTCTACCCTCCGCACC-3' (forward) and 5'-AGGAAGTGAAATCGTGCTGA-3' (reverse). The primers for GAPDH were: 5'-CCACATCGCTCAGACACCAT-3' (forward) and 5'-ACCAGGCGCCCAATACG-3' (reverse). The relative expression of LINC01420 was calibrated by GAPDH expression.

Cell transfection

LINC01420 expression level was reduced in CRC cells after transfection with small inter fering RNAs (siRNA) by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). All siRNAs listed in our manuscript were ordered from GenePharma Co., Ltd. (Shanghai, China), and transfection efficiency was detected by qRT-PCR two days after transfection.

Bioinformatics analysis

The binding sites corresponding to their respective lncRNA and miRNA were predicted by starBase (https://http://starbase.sysu.edu.cn/) and miRanda (http://www.microrna.org/microrna/home.do). StarBase was designed to decipher the interaction networks of lncRNAs, miRNAs, ceRNAs [15] in tumor groups. miRanda was used to forecast microRNA targets based on the miRanda algorithm and expression features in tumor groups [16].

Establishment of PPI networks and analysis of modules

STRING was used to evaluate PPI networks and was conducted to sketch DEGs (differentially expressed genes) and used to figure out the unknown interaction between DEGs. The detailed selection principle was referred to as follows: confidence score was more than 0.4, and maximal interactors number only represented none/query proteins. For PPI networks modules selection, we used Molecular Complex Detection (MCODE) in Cytoscape (version 3.6.1) and obtained the final results based on the principle as cutoff = 2, node score cutoff = 0.2, k-core = 2, and maximum depth = 100.

Separation of cytoplasm and nuclear RNA

The nuclear and cytoplasmic fractions of SW620 and SW480 cells were separated using a PARIS kit (Life Technologies) in accordance with the manufacturer's protocol. Firstly, the cells were washed gently with ice-cold PBS, twice. The cell lysate was incubated on ice for 5 min. After centrifuging at 500 g for 5 min at 4°C, the precipitate containing the nuclear RNA was isolated from the supernatant con-

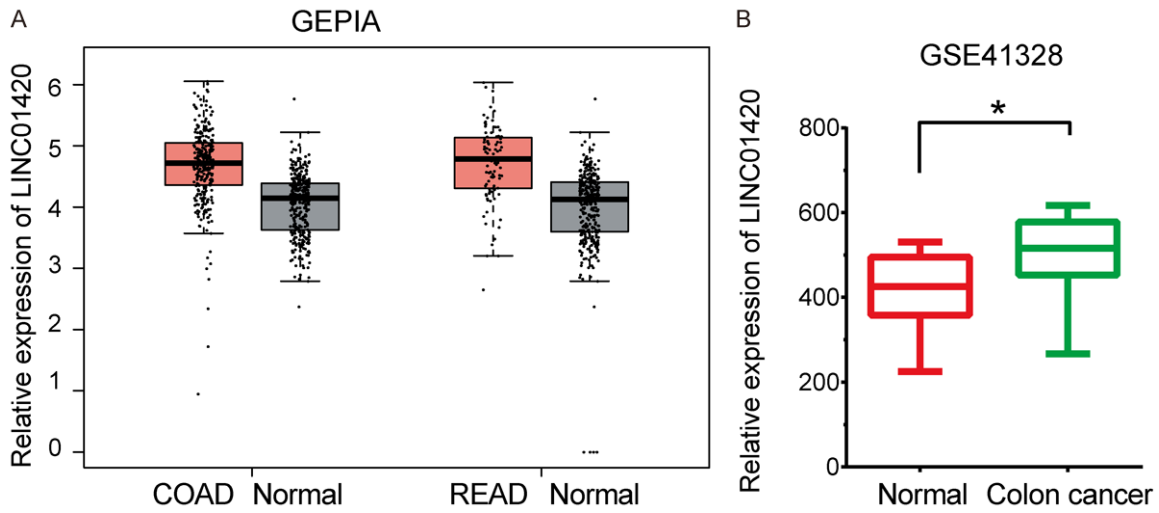

Figure 1. LINC01420 is up-regulated in colorectal cancer tissue and cells. A. LINC01420 was up-regulated in colon adenocarcinoma (COAD) or Rectum adenocarcinoma (READ) and matched normal tissues by analyzing GEPIA datasets. B. LINC01420 was up-regulated in CRC samples compared with non-tumor tissues by analyzing the GSE41328 dataset. *, P < 0.05.

taining the cytoplasmic RNA. Finally, the supernatant was carefully removed to a new 1.5 ml EP tube. The precipitate was washed with PBS twice and resuspended by nuclear storage buffer. Reverse transcription and RT-PCR (TB Green Premix Ex Taq II; TaKaRa) were performed with the extracted RNA.

Cell cycle and apoptosis assay

Cells were harvested 48 h after transfection. For cycle assay, cells were incubated with 0.03% Triton X-100 and propidium iodide (PI) (50 ng/mL) for 15 min; the percentage of cells in different phases of the cell cycle were measured with a FACScalibur flow cytometer (BD, CA, USA) and analyzed with ModFit software (Verity Software House, ME, USA). For apoptosis assay, cells were assayed with FITC Annexin V Apoptosis Detection Kit (BD, CA, USA) and analyzed by flow cytometry.

Statistical analysis

Our representative data were analyzed by SPSS 17.0 software (Chicago, IL, USA) and derived from more than three independent experiments. The differences existing in any two compared groups was determined by Student's *t*-test. The Kaplan-Meier assay and the log-rank test were applied to analyze overall survival. Significance was indicated by a *P*-value < 0.05.

Results

LINC01420 level is up-regulated in colorectal cancer tissues

Firstly, we detected the differential expression of lncRNAs in either colon adenocarcinoma (COAD) and matched normal tissues or Rectum adenocarcinoma (READ) and matched normal tissues using GEPIA datasets. As presented in **Figure 1A**, our data revealed that LINC01420 was up-regulated in both COAD and READ tissues compared to that in normal tissues (P < 0.001, **Figure 1A**). Then, an independent GEO dataset, GSE41328 based on the Affymetrix HG_U133 Plus 2 arrays were also used to confirm the conclusion from GEPIA database analysis (**Figure 1B**).

Up-regulated LINC01420 indicated poorly prognostic status and was an independent predictor for overall survival of CRC patients

Figure 2 showed the correlations between LINC01420 expression and clinical pathologic features. Up-regulated LINC01420 was markedly associated with advanced N stage (*P* < 0.05), M stage (*P* < 0.05), pathology classification (*P* < 0.05), vascular metastasis (*P* < 0.05) and lymph node metastasis (*P* < 0.05) in CRC patients. However, no relevance between LINC01420 expression and other characteris-

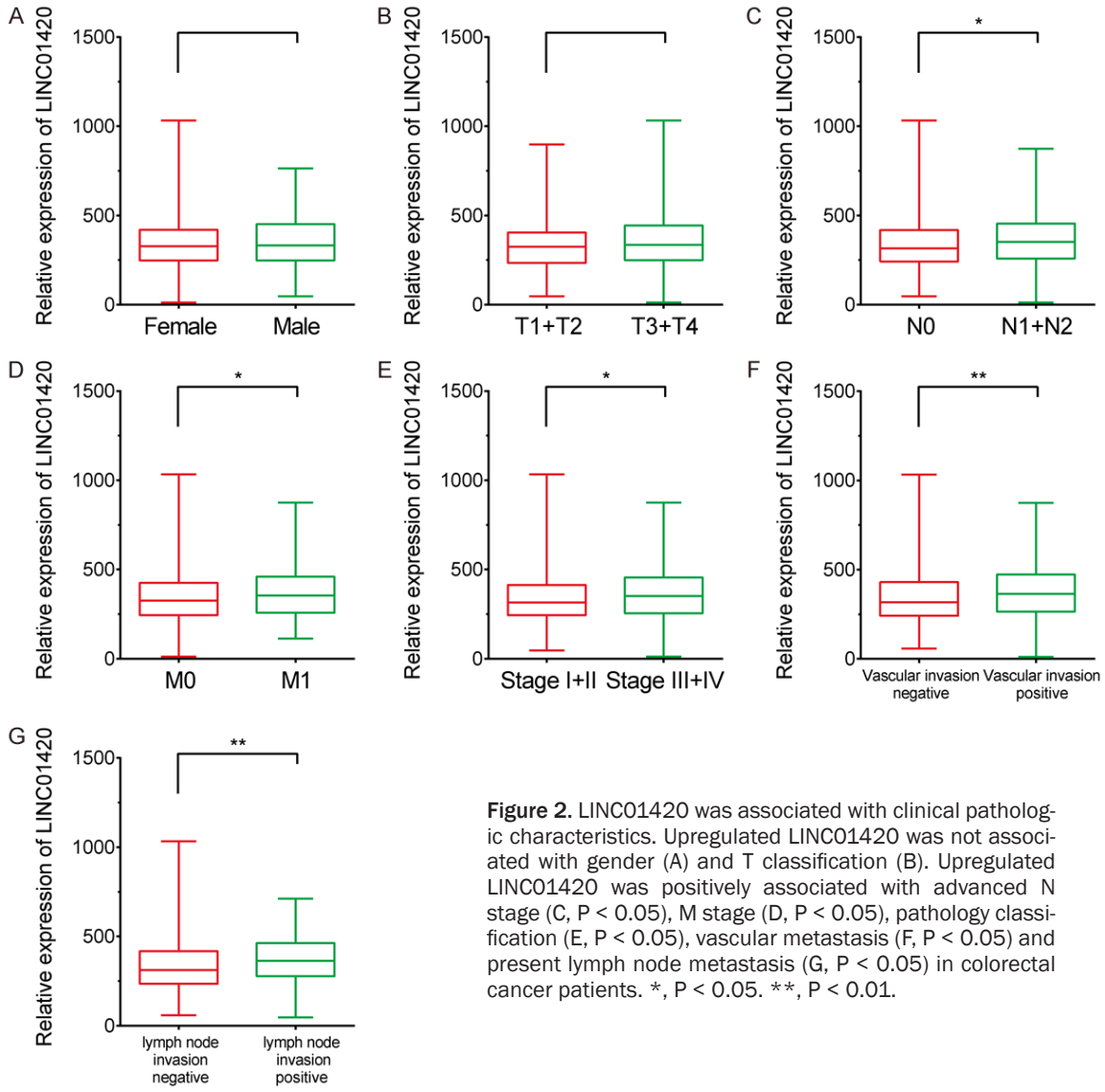

Figure 2. LINC01420 was associated with clinical pathologic characteristics. Upregulated LINC01420 was not associated with gender (A) and T classification (B). Upregulated LINC01420 was positively associated with advanced N stage (C, $P < 0.05$), M stage (D, $P < 0.05$), pathology classification (E, $P < 0.05$), vascular metastasis (F, $P < 0.05$) and present lymph node metastasis (G, $P < 0.05$) in colorectal cancer patients. *, $P < 0.05$. **, $P < 0.01$.

tics, including age and T systematics, was shown.

Moreover, we evaluated the implication of LINC01420 in prognostic patients with CRC using the TCGA database and R2: Genomics Analysis and Visualization Platform database. All CRC samples were classified into highly expressed, and lowly expressed LINC01420 groups in view of the average level of LINC01420 expression level. Our results showed that highly expressed LINC01420 was linked with a shorter overall survival time in CRC patients by TCGA database analysis (**Figure 3A**) and R2: Genomics Analysis and Visualization Platform database (**Figure 3B**). Taking the above results into consideration, the high expression of *LINC01420* can be regarded as an independently generated molecular risk for patients with CRC.

Co-expression analysis of LINC01420 and PPI modules

To identify the link between LINC01420 and PPI (Protein-Protein Interaction Networks) modules, we first calculated the correlation coefficient between each LINC01420 and mRNAs in CRC using the cBioPortal database (https://www.cbioportal.org/). The top 1000 correlated mRNAs were selected as the potential targets of LINC01420 in CRC. Furthermore, the PPI networks were constructed using the STRING database. As presented in **Figure 4**, our data

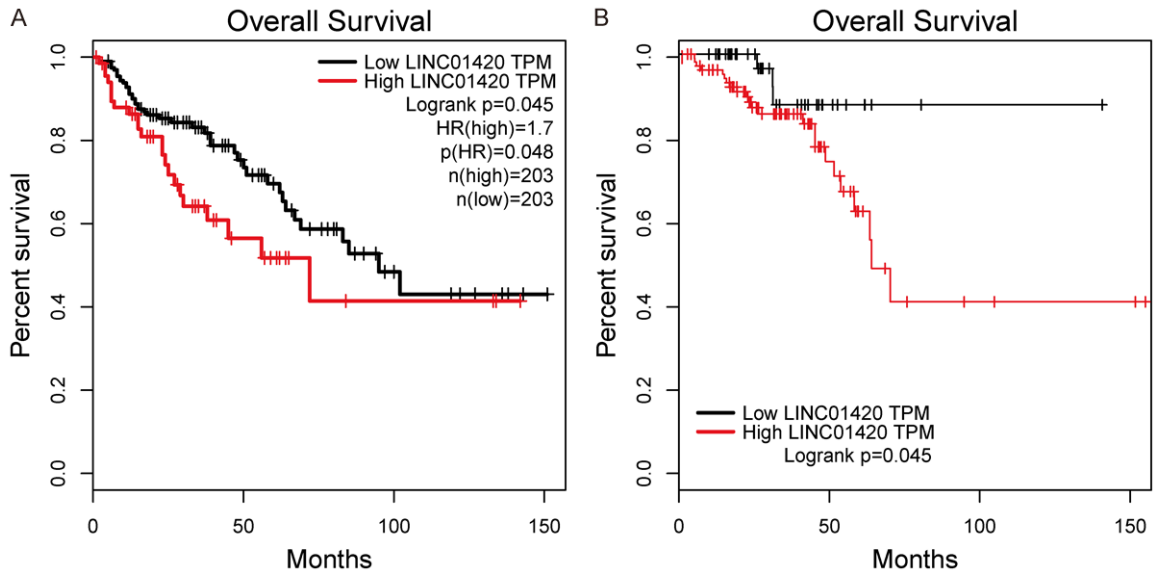

Figure 3. LINC01420 predicts poor prognosis. The up-regulated LINC01420 was significantly associated with the shorter overall survival time in patients with CRC by analyzing (A)TCGA and (B) R2: Genomics Analysis and Visualization Platform database.

showed that the PPI network contained 443 nodes and 1,386 edges.

Additionally, to identify the modules in the LINC01420 related PPI networks, we performed PPI modules network analysis by the MCODE plugin referring to degree cut off ≥ 3, the nodes with edges ≥ 2 core; the number of nodes ≥ 7). We identified four hub modules in the PPI network, respectively. The detailed integrated network listed is as follows: 37 nodes and 621 edges were shown in hub network 1 (**Figure 4A**), 25 nodes and 165 edges were indicated in hub network 2 (**Figure 4B**), 12 nodes and 59 edges were demonstrated in hub network 3 (**Figure 4C**), and 32 nodes and 123 edges were represented in hub network 4 (**Figure 4D**).

Bioinformatics analysis of LINC01420 in CRC

The GO analysis identified LINC01420 was involved in regulating translational initiation, transcription-coupled nucleotide-excision repair, phosphorylation, cristae formation, mRNA splicing, chromatin silencing, chromosome segregation, mitotic nuclear envelope disassembly, mitotic nuclear division, regulation of growth, and cell cycle (**Figure 5A**). The KEGG pathway analysis identified LINC01420 was involved in regulating ribosomes, RNA transport, carbon metabolism, pyrimidine metabolism, metabolic pathways, pentose phosphate pathway, RNA polymerase, and biosynthesis of antibiotics (**Figure 5B**).

LINC01420 positively regulated multiple cell cycle regulators in CRC

Bioinformatics analysis showed that LINC01420 was associated with regulating carbon metabolism through co-expressing DLAT, G6PD, GOT1, IDH3G, MTHFR, PFKP, PGK1, PRPS1, PRPS2, PDHA1, RGN, SDSL, and SDHA (**Figure 6A**). Very interestingly, our analysis also indicated that LINC01420 was involved in regulating cell cycle and proliferation through multiple cell cycle regulators in CRC, including DYNLT3, TPR, ZC3HC1, INCENP, STAG2, USP9X, NDC80, ZNF830, CASC5, CENPF, SKA1, KIF2DB, KIF11, ASPM, CETN2, OFD1, HAUS7, ANAPC13, BRCC3, ANAPC16, and ANAPC11 (**Figure 6B**).

To study the mechanisms of LINC01420 function in CRC cells, we performed, subcellular fractionation followed by qRT-PCR in SW620 and SW480 cells. The results showed that the LINC01420 level was higher in the cytoplasm than in the nuclear fraction suggested LINC01420 is a cytoplasm-located lncRNA (**Figure 7A**).

To validate the above findings, we conducted qRT-PCR to measure the downstream regulators' expression level in LINC01420-knock-

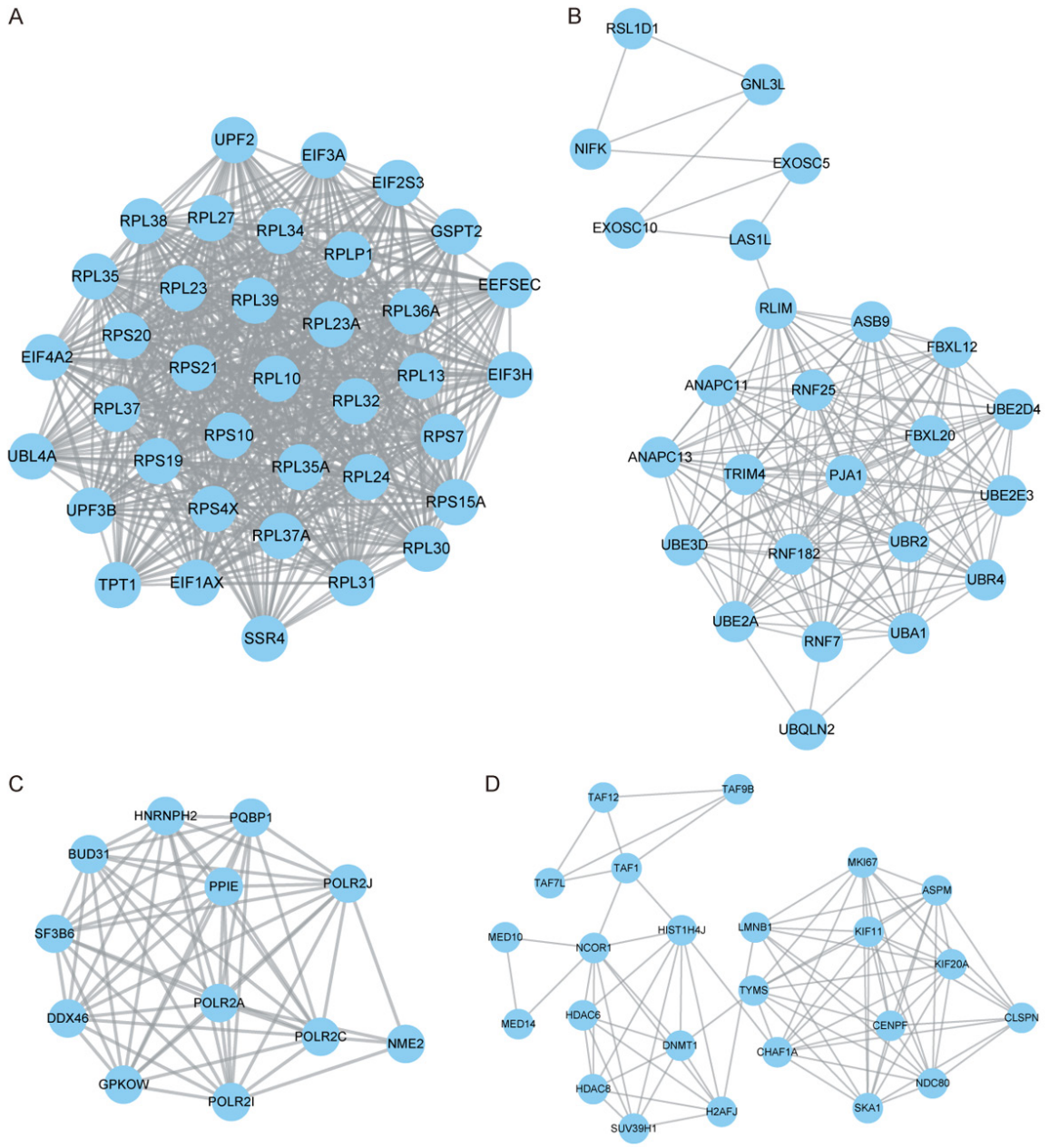

Figure 4. The PPI modules of LINC01420. A-D. Four hub modules in the PPI network were identified.

down CRC cells. The data showed that the reduction of LINC01420 dramatically suppressed CUL4B, TAF1, MCTS1, and BEX2 expression levels (**Figure 7B**).

LINC01420 promotes colorectal cancer cell proliferation

The prediction showed that LINC01420 participated in the pathway of cell proliferation and cell cycle modulation. Our data, for the first time, revealed that the change of LINC01420 expression exerted influences on cell proliferation of colorectal cancer and observed that reduction of LINC01420 led to strong inhibition of both SW480 and SW620 cell proliferation (**Figure 7C-F**).

Moreover, we detected the cell cycle and apoptosis after the LINC01420 knockdown in CRC cells. Phase analysis showed the percentage of cells in the G1 phase was increased, however, the percentage of cells in G2/M phase was

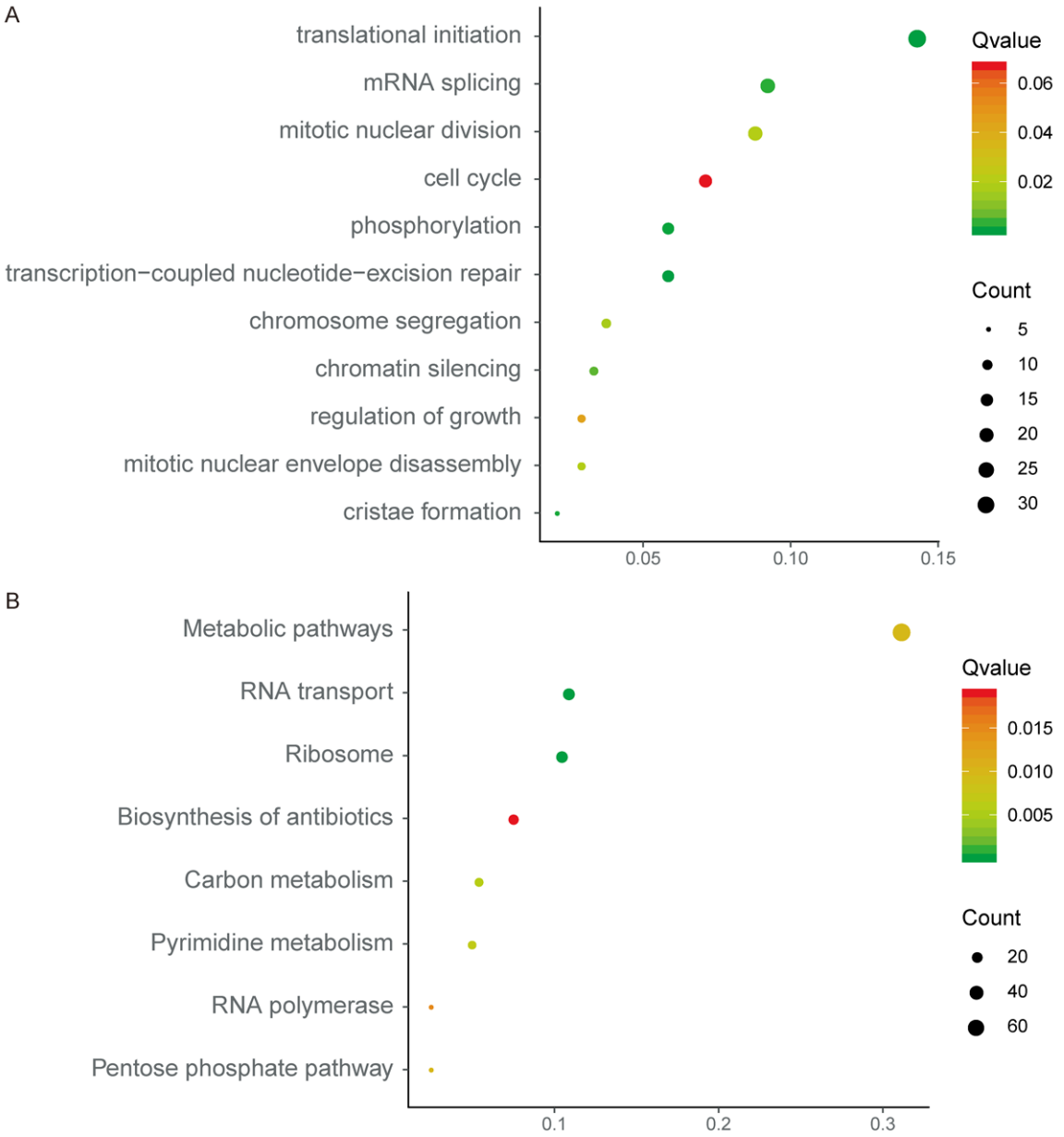

Figure 5. The GO and KEGG pathway analysis of LINC01420 in CRC. A. The GO analysis identified LINC01420 was involved in regulating translational initiation, transcription-coupled nucleotide-excision repair, phosphorylation, cristae formation, mRNA splicing, chromatin silencing, chromosome segregation, mitotic nuclear envelope disassembly, mitotic nuclear division, regulation of growth, and cell cycle. B. The KEGG pathway analysis identified LINC01420 was involved in regulating ribosome, RNA transport, carbon metabolism, pyrimidine metabolism, metabolic pathways, pentose phosphate pathway, RNA polymerase, and biosynthesis of antibiotics.

significantly reduced in SW620 and SW480 cells (**Figure 8A-D**). The flow-cytometry analysis revealed the apoptosis rate in the LINC01420 knockdown group was significantly increased compared to that in the control group, suggested that LINC01420 knockdown could promote CRC cell apoptosis (**Figure 8E-H**).

Discussion

It is well known for a long time that lncRNAs are noncoding genes [17]. However, with the development of deep ribosome profiling sequencing (Ribo-Seq) and mass spectrometry technology, a branch of lncRNAs had been demonstrated to have the ability to encode small peptides with

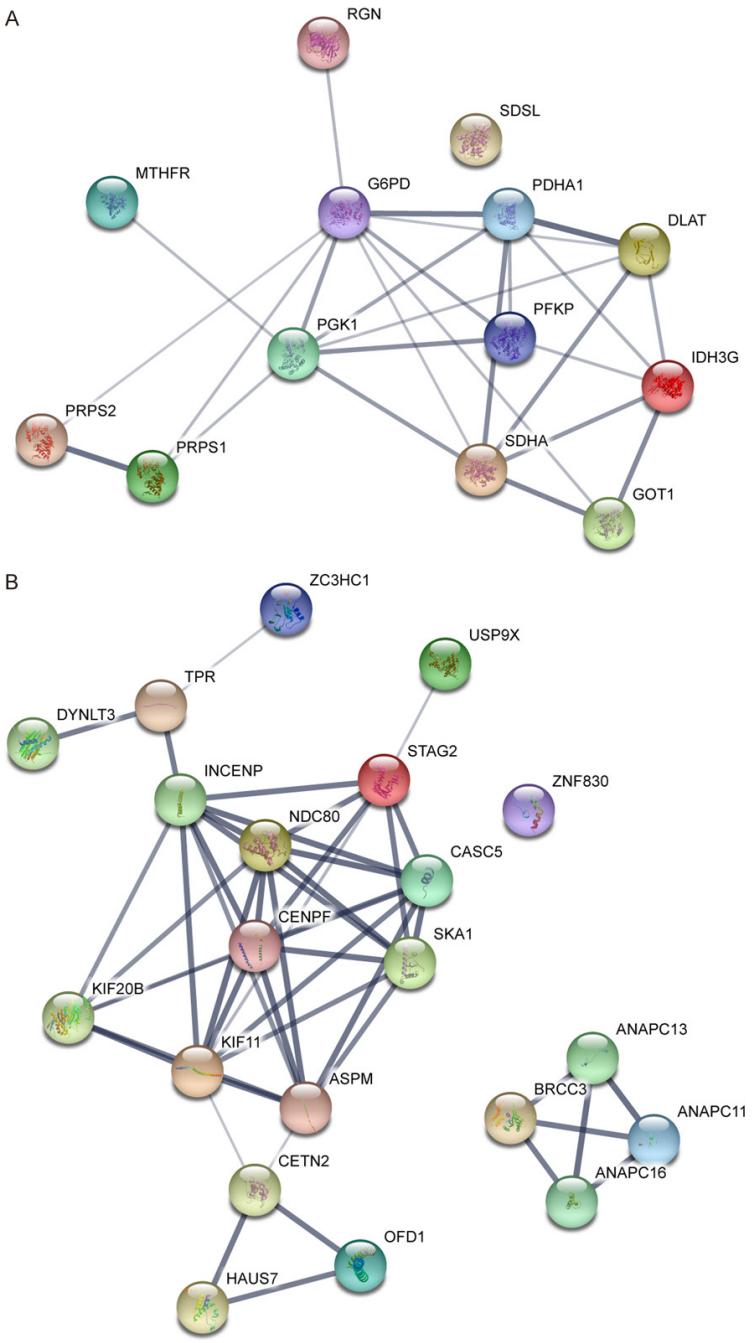

Figure 6. LINC01420 positively regulated cell cycle regulators by using bioinformatics analysis. A. Bioinformatics analysis showed that LINC01420 was associated with regulating carbon metabolism through co-expressing DLAT, G6PD, GOT1, IDH3G, MTHFR, PFKP, PGK1, PRPS1, PRPS2, PDHA1, RGN, SDSL, and SDHA. B. Bioinformatics analysis showed that LINC01420 was involved in regulating cell cycle and proliferation through multiple cell cycle regulators in CRC, including DYNLT3, TPR, ZC3HC1, INCENP, STAG2, USP9X, NDC80, ZNF830, CASC5, CENPF, SKA1, KIF2DB, KIF11, ASPM, CETN2, OFD1, HAUS7, ANAPC13, BRCC3, ANAPC16, and ANAPC11.

no more than 100 amino acids [18]. These peptides and lncRNAs functioned in human disease progress by affecting multiple signaling pathways [19]. Matsumoto et al. demonstrated that SPAR polypeptide, encoded by LINC00961; like regulating skeletal muscle regeneration through mTORC1 activity [20]. Huang et al. reported lncRNA HOXB-AS3-encoded a peptide that could suppress cell growth of colon cancer [21]. LINC01420 functioned importantly, in the progression of human nasopharyngeal carcinoma, as described before [22]. Very interestingly, D'Lima et al. found that LINC01420 encoded a sort of microprotein, non-annotated P-body dissociating polypeptide (NoBody), and interplayed with the mRNA decapping complex through binding to EDC4 [23]. However, the prognostic value and function roles of LINC01420 in CRC remain largely unclear.

CRC, as one of the most prevalent malignant tumor types, was the fourth primary inducer of cancer-induced mortality all over the world [1]. However, the 5-year survival rate of CRC patients with recurrence and metastasis remained as low as 10%. Pressing urgency to uncover a new biomarker for CRC is thus essential. The present study revealed that the LINC01420 level was obviously enhanced in CRC samples normalized to that in normal samples. Remarkably, our literature showed that higher expression of LINC01420 had an association with clinical stage, metastasis of lymph nodes, distant metastasis, and poorly differentiated extent in CRC patients. Higher expression of LINC01420 exhibited significant association with shorter overall survival time in CRC patients after both datasets

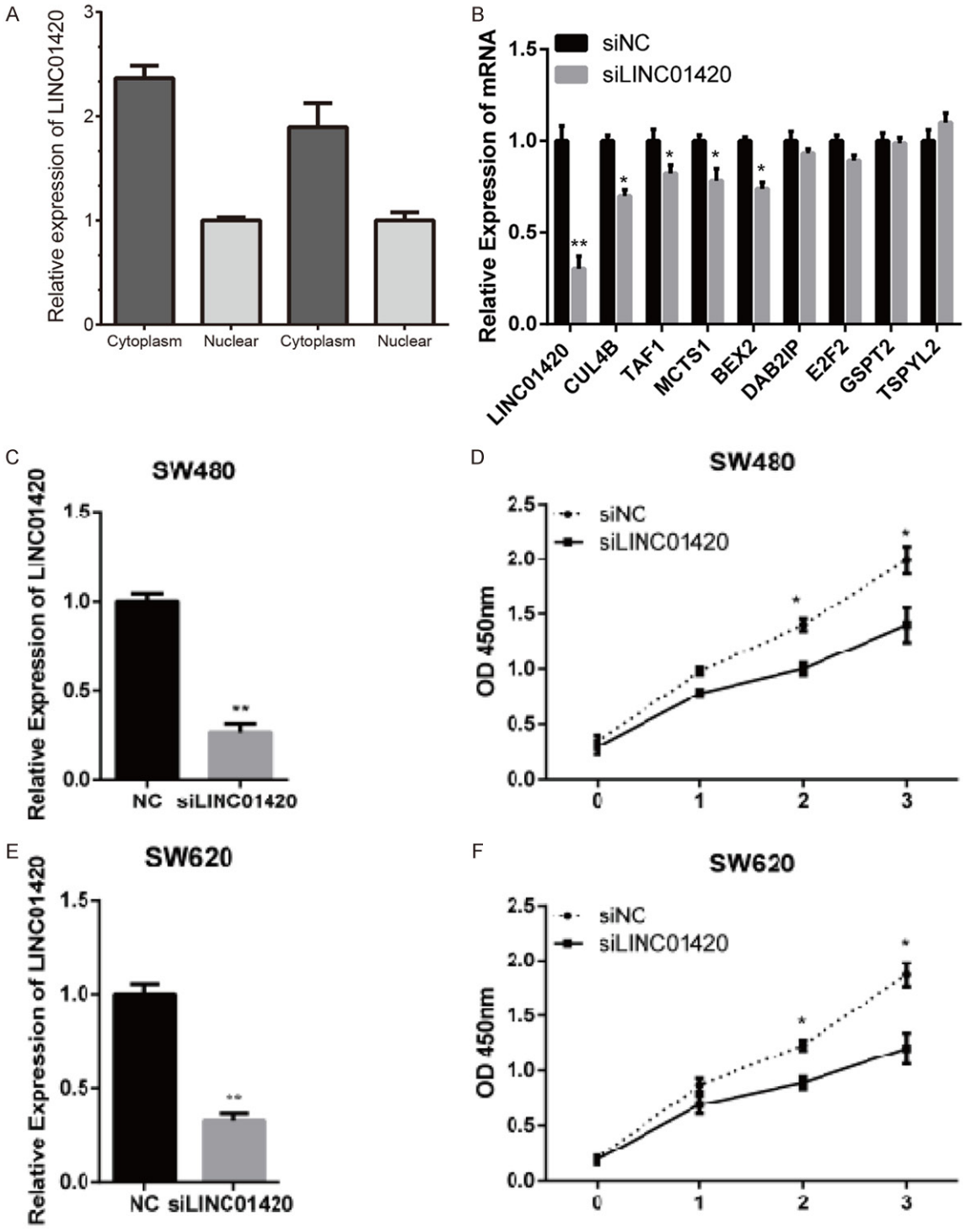

Figure 7. LINC01420 promotes colorectal cancer cell proliferation. A. qRT-PCR showed LINC01420 level was higher in the cytoplasm than in the nuclear suggested. B. qRT-PCR showed that the silencing of LINC01420 significantly suppressed the expression of CUL4B, TAF1, MCTS1, and BEX2. C, D. The expression levels of LINC01420 after transfecting with siLINC01420 was detected using RT-PCR assay in SW620 and SW480 cell. E, F. CCK-8 assays showed that knockdown of LINC01420 strongly inhibited cell proliferation of SW620 and SW480 cells.

analysis. All of the above data indicated that LINC01420 was a probable indicator for CRC.

Recently, disorders of cell metabolism has become a main feature of cancer. Reprogr-

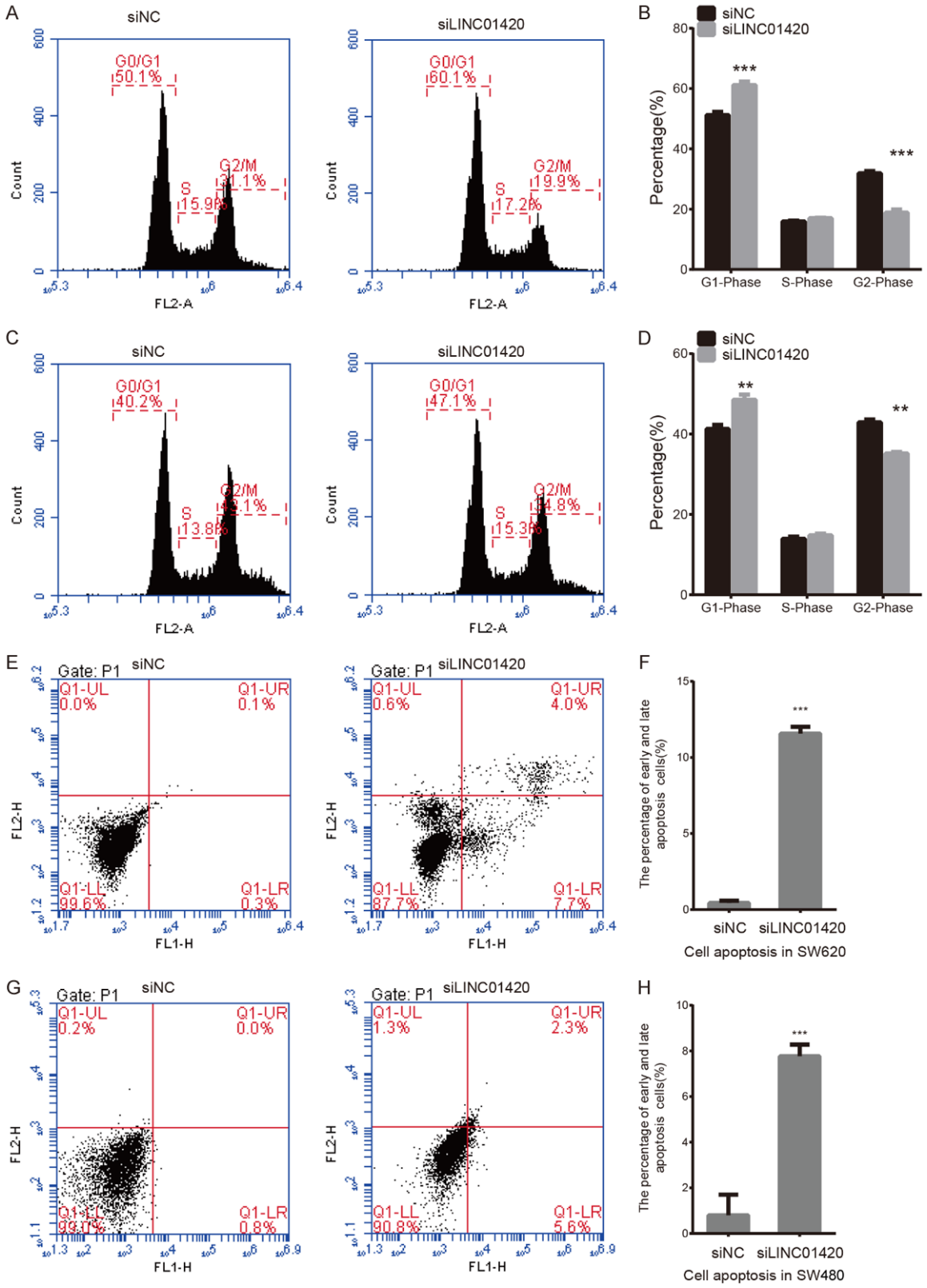

Figure 8. LINC01420 promotes colorectal cancer cell cycle and inhibite cell apoptosis. A-D. Knockdown of LINC01420 significantly induced the G1 phase, and reduced G2/M phase in (A, B) SW620 and (C, D) SW480 cells. E-H. Knockdown of LINC01420 significantly induced apoptosis rate in (E, F) SW620 and (G, H) SW480 cells.

amming of the metabolic pathways of the core cells by cancer cells could supply energy, anaplerotic precursors, and reduce the equivalent substances needed to sustain tumor growth [24]. The dysregulation of cellular metabolism could significantly modulate the proliferation, apoptosis, differentiation, and metastasis through multiple signalings, such as the Wnt pathway, and KRAS signaling [25]. Interestingly, we found that LINC01420 was associated with the regulation of carbon metabolism. A series of metabolism regulators significantly co-expressing with LINC01420 in CRC, including DLAT, G6PD, GOT1, IDH3G, MTHFR, PFKP, PGK1, PRPS1, PRPS2, PDHA1, RGN, SDSL, SDHA, PFKP and PGK1 are important enzymes in the glycolysis pathway, which were reported to be overexpressed in multiple human cancers, i.e., prostate cancer and CRC. Previous studies had demonstrated that PGK1 participated in the process of CRC proliferation and metastasis regulation [26]. PFKP together with other glycolysis enzymes, such as HK3, PKM, ENO1, HK2, PGAM1, GAPDH, ALDOA, GPI, TPI1, and HK1, were found to be up-regulated in CRC samples in the presence of high CIMP after comparison with that in CRC samples without CIMP [27]. Aberrant cell cycle progression functioned importantly and impelled human cancer cell proliferation. Interestingly, this study showed that LINC01420 was also involved in regulating cell cycle progression in CRC.

The hidden functions of LINC01420 in CRC remain elusive. The present study conducted a loss-of-function assays using a specific siRNA against LINC01420. Our data revealed that the reduction of LINC01420 significantly suppressed cell proliferation and cell cycle progression. However, the results also revealed that knockdown of LINC01420 significantly induced cell apoptosis in CRC cells. Interestingly, we found that knockdown of LINC01420 reduced a series of cell cycle regulator expression levels, such as CUL4B, TAF1, MCTS1, and BEX2. The functions of these genes in cancers had been revealed by multiple studies. For instance, CUL4B was up-regulated in multiple sorts of cancer, as previously described. CUL4B expression, as Wang et al. reported, was greatly forced in NSCLC cell lines. Reduced CUL4B could retard NSCLC cell proliferation, migration, and invasion [28]. TAF1 is a coactivator of AR that enhances the activity of AR in prostate cancer [29]. MCTS1 was revealed to be an oncogene and exhibited a critical role in cell cycle progression [30]. MCTS1 modulates the MAPK pathway and acts as a translational activator [31]. BEX2 was identified to be realated with glioblastoma [32], glioma [33], and breast cancer development [34]. As previous studies showed, BEX2-caused cell growth of human glioblastoma via the NF-κB signaling pathway [32]. Emerging research revealed that BEX2 exerted a promoting effect on colorectal cancer cell proliferation [35].

Conclusion

Overexpression of LINC01420 is demonstrated in colorectal cancer tissues and cell lines and is related to clinical progress. Moreover, LINC01420 induced colorectal cancer cell proliferation and cell cycle changes via modulating multiple cell cycle regulators.

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Disclosure of conflict of interest

None.

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