European Review for Medical and Pharmacological Sciences 2020; 24: 10526-10534

LncRNA LINC01278 accelerates colorectal cancer progression *via* miR-134-5p/KDM2A axis

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Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) play vital roles in the pathogenesis and development of multiple cancers, including colorectal cancer (CRC). Nevertheless, the regulatory mechanisms of LINC01278 in CRC remain unknown. Our research aims to identify the regulatory mechanisms of LINC01278 in CRC.

PATIENTS AND METHODS: The expression of LINC01278 was examined by quantitative real-time polymerase chain reaction (RT-qPCR). StarBase and TargetScan websites were used to predict the interaction between miR-134 and LINC01278 or KDM2A, which was further confirmed by Dual-Luciferase reporter assay and RNA immunoprecipitation (RIP) assay. Cell viability, migration, and invasion were detected by Cell Counting Kit-8 (CCK-8) and transwell assays.

RESULTS: LINC01278 was upregulated in CRC tissues and cell lines, and knockdown of LINC01278 suppressed CRC cell progression. In addition, LINC01278 inhibited miR-134 expression by direct interaction, and the inhibition of miR-134 abolished the suppressive effects of LINC01278 knockdown on viability, migration, and invasion of CRC cells. Furthermore, KDM2A was confirmed to be a target gene of miR-134. Overexpression of KDM2A facilitated the tumorigenesis of CRC, while this effect was reversed by the upregulation of miR-143. Finally, it was demonstrated that miR-134 inhibitor reversed the shLINC01278-mediated inhibitory effect on KDM2A expression.

CONCLUSIONS: Our study demonstrated that LINC01278 upregulated KDM2A to promote CRC progression by interacting with miR-143, suggesting that LINC01278 might be a new therapeutic target of CRC.

Key Words:
LINC01278, MiR-134-5p, KDM2A, Colorectal cancer.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth fatal malignant neoplasm worldwide[1,2]. Increasing evidence has shown that genetic or epigenetic abnormalities are associated with the development of CRC[3]. Although great progress has been made in the treatment, such as surgery, chemotherapy, and radiotherapy, the overall survival rates of CRC patients are still low[4,5]. Therefore, it is urgent to develop novel therapeutics for the treatment of CRC.

Long non-coding RNAs (lncRNAs) are a class of RNA transcripts longer than 200 nucleotides in lengths, which have no protein-coding ability[6,7]. Increasing evidence has indicated that lncRNAs are involved in the physiological and pathological processes of various cancers[8,9]. Huang et al[10] indicated that LINC01278 contributed to the development of hepatocellular carcinoma *via* the miR-1258/Samd2/3 axis. Qu et al[11] illustrated that LINC01278 knockdown restrained proliferation and favored apoptosis in osteosarcoma cells *via* miR-133a-3p/PTHR1 axis. Lin et al[12] showed that LINC01278 positively regulated the expression of DNM3 to suppress thyroid carcinoma progression. However, the biological role of LINC01278 in CRC remains unknown.

MicroRNAs (miRNAs) are another type of endogenous non-coding RNAs with a length of 18–25 nucleotides[13]. Dysregulation of miRNAs plays a vital role in the occurrence and development of various cancers types. Qin et al[14] reported that miR-134 inhibited the tumorigenesis of non-small cell lung cancer by interacting with ITGB1. Wang et al[15] found that miR-134 suppressed the proliferation of retinoblastoma cells by regulating SMAD6. Fu et al[16] pointed out that TTN-AS1 suppressed cell apoptosis by regulating miR-134 in osteosarcoma cells. Nevertheless, the mechanism by which miR-134 regulates CRC is largely unknown.

Our research proposed to elucidate the role and underlying molecular mechanism of LINC01278 in CRC. The results demonstrated that LINC01278

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upregulated KDM2A expression by absorbing miR-134 to promote the progression of CRC. These findings suggested that LINC01278 might serve as a potential therapeutic target for CRC treatment.

Patients and Methods

Clinical Samples

Human CRC tissues and adjacent healthy tissues were obtained from the Wujin Hospital Affiliated with Jiangsu University. A total of 30 patients were included in this study between February 2017 and August 2019 according to strict inclusion and exclusion criteria. Inclusion criteria: (1) patients diagnosed as CRC by pathologic examinations. (2) patients were not treated preoperatively. Exclusion criteria: (1) patients have other diseases. (2) patients were treated prior to admission. All patients signed the written informed consent and this research was approved by the Ethics Committee of Wujin Hospital Affiliated with Jiangsu University.

Cell Culture

Human colon immortalized cell line (FHC), CRC cell lines (DLD1, SW480, HCT116, and HT29), and 293T cells were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM; Corning Life Sciences, MA, USA), and supplemented with 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) in a humidified atmosphere containing 5% CO_2 at 37°C.

Cell Transfection

Short hairpin RNA (shRNA) targeting LINC01278 (shLINC01278) with control (shNC), miR-134 mimics with control (NC mimics), and miR-134 inhibitor with control (NC inhibitor) were purchased from RiboBio (Guangzhou, China). KDM2A overexpression plasmid (pcDNA3.1/KDM2A), LINC01278 overexpression plasmid (pcDNA3.1/LINC01278) and control (pcDNA3.1) were obtained from Sangon Biotech (Shanghai, China). The transfection was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

RT-qPCR

TRIzol Reagent (Thermo Fisher Scientific, Waltham, MA, USA) was employed to isolate total RNA from tissues and cells. PrimeScript RT reagent kit (TaKaRa, Dalian, China) was used to reverse RNA to complementary DNA (cDNA). The RT-qPCR was performed by using SYBR qPCR Master Mix (Vazyme, Nanjing, China). The relative expression of genes was measured using the $2^{-\Delta\Delta Ct}$ method. GAPDH and U6 were used as endogenous controls.

The primer sequences used for RT-qPCR were as follows: LINC01278 forward: 5'-CCATACGCT ACGATCGAGAC-3' and reverse: 5′-TCTGGGTTACCTTAACGCATA-3′; miR-134-5p forward: 5'-ACACTGCATCCTGGCAATTC-3' and reverse: 5'-CGTGGTGAATCGAGACTCAC-3'; KDM2A forward: 5′-CCGATTGTGTCAGGAGCCAG-3′ and reverse: 5′-CACAAATTCCCATCATTCCC-3′; GAPDH forward: 5′-CCAAAATCAGATGGGGCAATGCTGG-3' and reverse: 5'-TGATGGCATGGACTGTGGTCATTCA-3′; U6 forward: 5'-CTCGCTTCGGCAGCACA-3′ and reverse: 5′- AACGCTTCACGAATTTGCGT-3′.

Luciferase Reporter Assay

StarBase and targetScan websites were used to predict the binding sites between miR-134 and LINC01278 or KDM2A. Wild-type LINC01278 (LINC01278-WT), mutant-type (LINC01278-Mut), wild-type KDM2A(KDM2A-WT) and mutant-type (KDM2A-Mut) were constructed by GenePharma (Shanghai, China). The reporter plasmids were co-transfection with miR-134 mimics or NC mimics *via* Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). After 48 h, the Dual-Luciferase reporter assay system (Promega, Madison, WI, USA) was used to detect Luciferase activity.

CCK-8

DLD1 and SW480 cells were seeded into 96-well plates with $5x10^5$ cells/well. Cell viability was detected at 0, 24, 48, and 72 hours. 10 μL CCK-8 solution (Dojindo, Molecular Technologies, Kumamoto, Japan) was added into each well for another 4 h. The absorbance at 450 nm was determined by a microplate reader (Bio-Rad, Hercules, CA, USA).

Transwell Assay

For migration assay, transfected cells (1×10^5) in medium without serum were placed in the upper chamber. The culture medium was added to the lower chamber. After 24h culture, and the cells in the lower chamber were fixed with methanol and dyed with crystal violet. For invasion assay, the insert was coated with Matrigel (BD Biosciences, Franklin Lakes, NJ, USA). Besides that, all

other steps are the same. Migrated and invaded cells were recorded under an inverted microscope (Olympus, Tokyo, Japan).

RNA Immunoprecipitation (RIP) Assay

RIP assay was conducted by Magna RIP Kit (Millipore, Billerica, MA, USA). Cell lysates were incubated in RIP buffer with magnetic beads coated with Ago2 antibodies (Millipore, Billerica, MA, USA). IgG was used as a negative control. After incubation, the co-precipitated RNA was eluted from the magnetic beads, purified and tested by RT-qPCR assay.

Statistical Analysis

All experiments were conducted three times. Data were presented as mean ± standard deviation (SD). SPSS 17.0 (Chicago, IL, USA) software and Graph-Pad Prism 6 were employed for statistical analysis. Student's *t*-test and one-way analysis of variance (ANOVA) were performed to assess the differences. Pearson analysis was applied for analyzing the correlations between genes. $p < 0.05$ was considered statistically significant.

Results

LINC01278 Was Upregulated in CRC Tissues and Cell Lines

The expression level of LINC01278 was investigated in CRC tissues, and the results indicated that LINC01278 expression was highly expressed in CRC tissues compared with that in adjacent normal tissues (Figure 1A). Similarly, LINC01278 expression was upregulated in CRC cell lines, especially in DLD1 and SW480 cells (Figure 1B). In addition, it was found that LINC01278 expression was associated with histological grade, tumor stage, and lymph node metastasis, while there was no association with age or sex (Table I). Taken together, these results suggested that LINC01278 might act as a tumorigenic gene in CRC.

Knockdown of LINC01278 Inhibited Progression of CRC

To confirm whether LINC01278 knockdown affected the development of CRC, DLD1 and SW480 cells were transfected with shNC and shLINC01278. RT-qPCR was conducted to verify the transfection efficiency (Figure 2A). CCK-8 assay revealed that knockdown of LINC01278 remarkably decreased the proliferation of DLD1 and SW480 cells (Figure 2B). Transwell assays showed that the depletion of LINC01278 inhibited migration and invasion of CRC cells (Figure 2C and D). In summary, knockdown of LINC01278 inhibited the proliferation, migration and invasion of CRC.

LINC01278 Was a Target of MiR-134 in CRC

Through using starBase (http://starbase.sysu.edu.cn), we observed that LINC01278 harbored the binding sites of miR-134 (Figure 3A). As shown in figure 3B, miR-134 mimics significantly weakened the Luciferase activity of wild-type LINC01278, while had no influence on mutant LINC01278. Moreover, RIP assay showed that LINC01278 and miR-134 were markedly enriched in Ago2 group

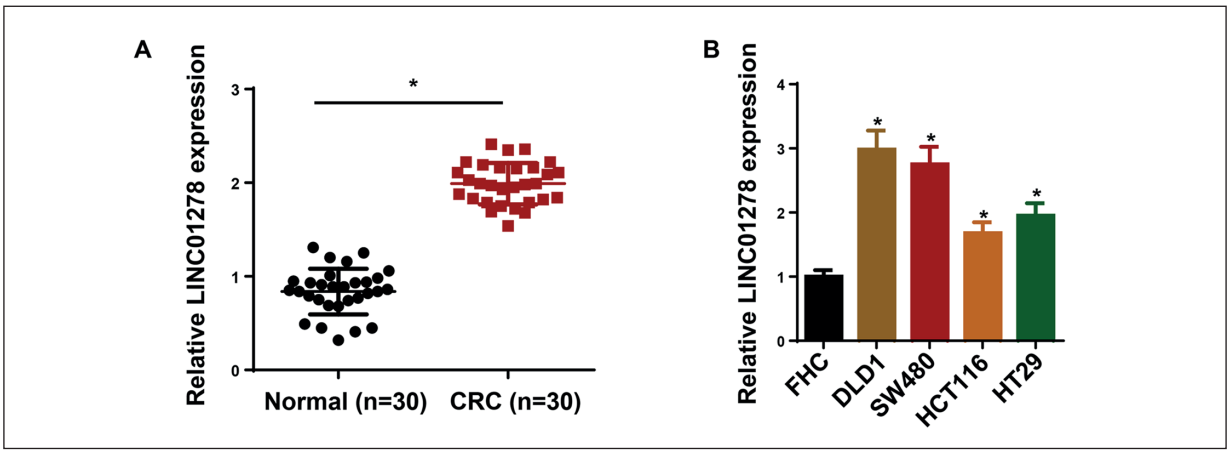

Figure 1. LINC01278 was upregulated in CRC tissues and cells. **A**, The expression of LINC01278 in CRC tissues and adjacent normal tissues were measured by RT-qPCR. **B**, The expression of LINC01278 in CRC cell lines (DLD1, SW480, HCT116 and HT29) and Human colon immortalized cell line (FHC) were observed by RT-qPCR. The data were presented as mean ± SD (*$p < 0.05$).

Table I. Association between LINC01278 mRNA expression levels and clinicopathological features in patients with CRC.

Clinicopathological features	Number	Expression of LINC01278		*p*-value
		High	Low	
Age, years				0.358
≤ 50	14	7	7	
> 50	16	9	7	
Sex				0.473
Male	18	8	10	
Female	12	7	5	
Histological grade				0.016
Well/Moderate	20	8	12	
Poor	10	8	2	
Tumor stage				0.024
I-II	19	8	11	
III-IV	11	8	3	
Lymph node metastasis				0.013
Positive	12	9	3	
Negative	18	8	10	

than in IgG group (Figure 3C). Furthermore, the miR-134 expression was lowly expressed in CRC tissues (Figure 3D), and negatively correlated with LINC01278 expression (Figure 3E). RT-qPCR indicated that LINC01278 overexpression significantly decreased miR-134 expression (Figure 3F). Taken together, these data illustrated that LINC01278 inhibited miR-134 expression by direct interaction.

Silencing of MiR-134 Partially Restored shLINC01278-Attenuated Progression of CRC

To investigate whether LINC01278 exerted its biological function by regulating miR-134, DLD1 and SW480 cells were transfected with shNC, shLINC01278, shLINC01278 + miR-134 inhibitor. RT-qPCR revealed that miR-134 inhibitor re-

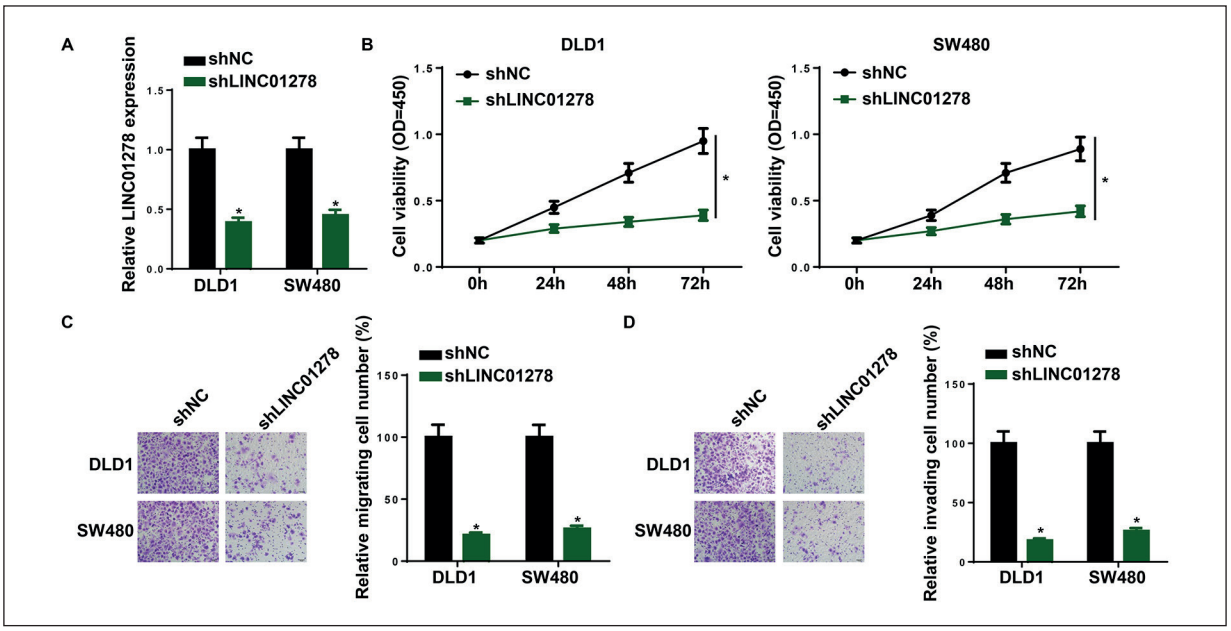

Figure 2. Knockdown of LINC01278 inhibited progression of CRC. **A**, The expression of LINC01278 was detected in DLD1 and SW480 cells transfected with shNC or shLINC01278 by RT-qPCR. **B**, After knockdown of LINC01278 expression, cell proliferation was assessed by CCK-8. **C**, **D**, Transwell assay was used to detect cell migration and invasion of DLD1 and SW480 cells transfected with shNC or shLINC01278 (magnification ×200). The data were presented as mean ± SD (*$p < 0.05$).

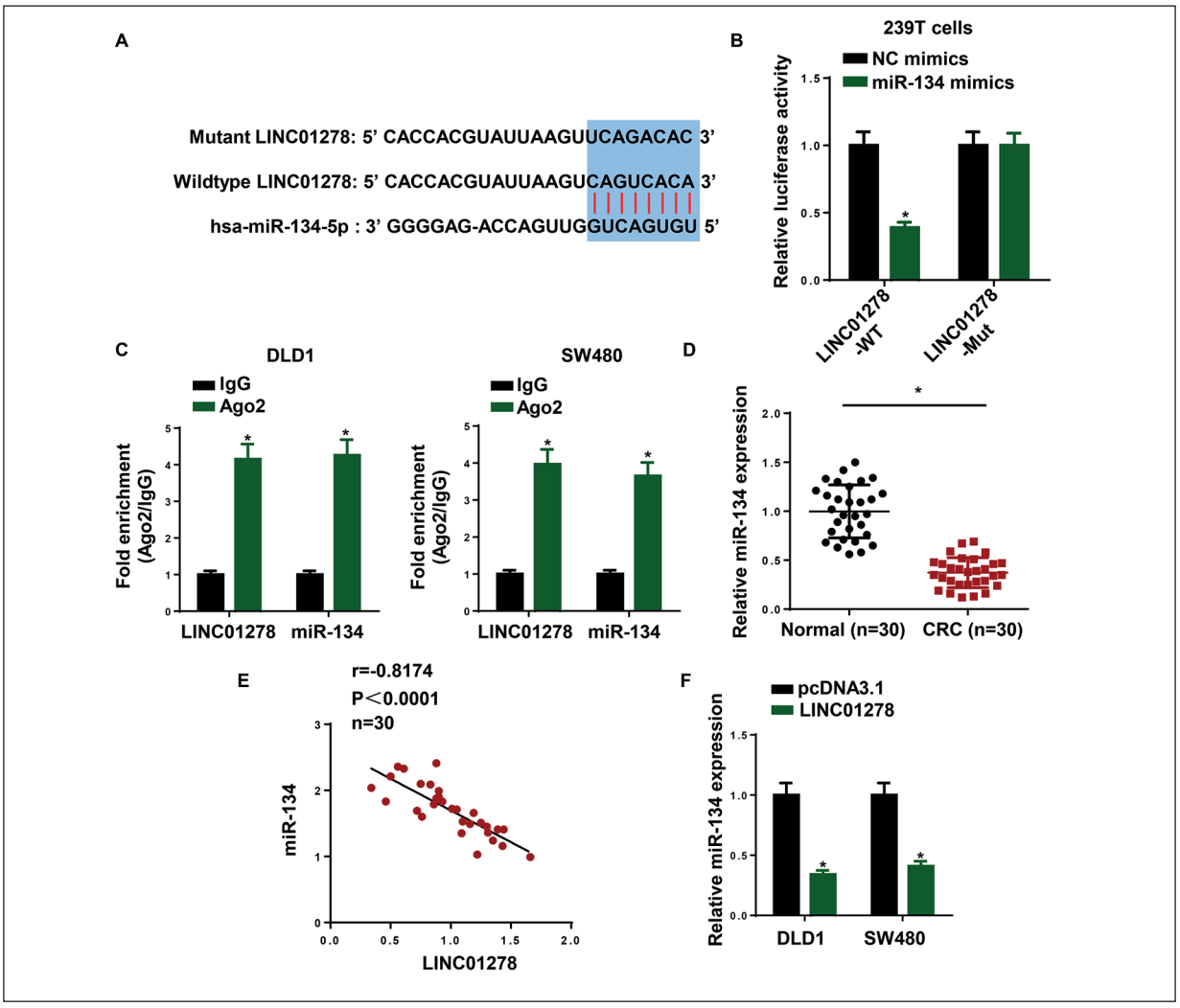

Figure 3. LINC01278 was a target of miR-134 in CRC. **A**,The predicted binding sites of LINC01278 and miR-134. **B**, The relative Luciferase activity was detected in 293T cells co-transfected with LINC01278-WT or LINC01278-Mut and miR-134 or NC mimics. **C**, The RIP assay was performed to explore the relationship between LINC01278 and miR-134. **D**, The level of miR-134 in CRC tissues and adjacent normal tissues were detected by RT-qPCR. **E**, The correlation between LINC01278 and miR-134 expression was evaluated by Pearson's correlation analysis. **F**, MiR-134 expression in DLD1 and SW480 cells transfected with pcDNA3.1 or LINC01278 were detected by RT-qPCR. The data were presented as mean ± SD (*$p < 0.05$).

versed the promotive effect of LINC01278 knockdown on the expression of miR-134 (Figure 4A). Subsequently, functional analyses revealed that shLINC01278 suppressed viability, migration and invasion of CRC cells, whereas the inhibitory effects were abolished by miR-134 inhibitor (Figure 4B-D). Overall, LINC01278 accelerated CRC cell progression by absorbing miR-134.

MiR-134 Interacted with KDM2A

Using TargetScan (http://www.targetscan.org), KDM2A was predicted to be a downstream target of miR-134 (Figure 5A). Subsequently, Luciferase reporter assay indicated that miR-134 mimics weakened the Luciferase activities of wild-type KDM2A but had no effect on the Luciferase activities of mutant KDM2A in 293T cells (Figure 5B). Meanwhile, the levels of miR-134 and KDM2A were higher in Ago2 group than that in IgG group. (Figure 5C). Moreover, the expression of KDM2A was highly expressed in CRC tissues (Figure 5D), and the levels of KDM2A was negatively correlated with the levels of miR-134 in CRC tissues (Figure 5E). The inhibition of miR-134 distinctly upregulated KDM2A expression in DLD1 and SW480 cells (Figure 5F). These

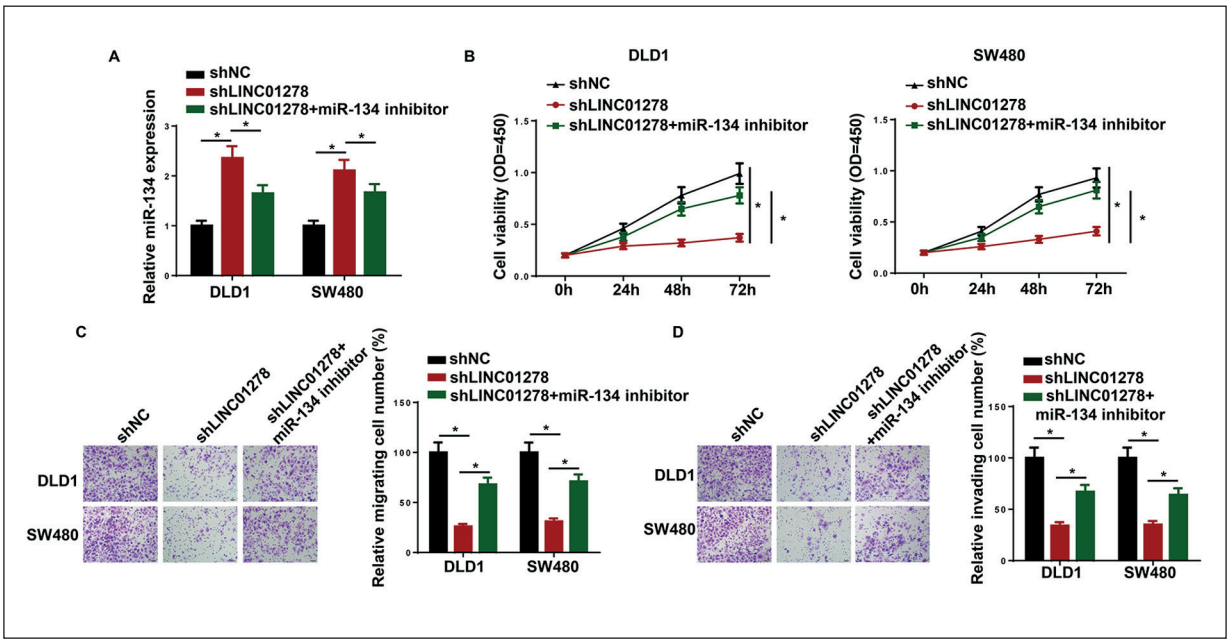

Figure 4. Silencing of miR-134 partially restored shLINC01278-attenuated progression of CRC. **A**, MiR-134 expression in DLD1 and SW480 cells transfected with shNC, shLINC01278, shLINC01278+ miR-134 inhibitor was detected by RT-qPCR. **B-D**, CCK-8 assay and transwell assay (magnification ×200) were used to detect viability, migration and invasion of DLD1 and SW480 cells transfected with shNC, shLINC01278, shLINC01278+miR-134 inhibitor. The data were presented as mean ± SD (*$p < 0.05$).

data indicated that KDM2A was a direct target of miR-134 in CRC cells.

LINC01278 Promoted KDM2A Expression by Acting as a ceRNA of MiR-134 in CRC Cells

To further explore whether miR-134 regulated CRC progression through KDM2A, KDM2A was introduced into miR-134-overexpressing DLD1 cells. Firstly, it was demonstrated that overexpression of KDM2A reversed the inhibitory effect of miR-134 overexpression on KDM2A expression (Figure 6A). Functional assays revealed that the effects of KDM2A overexpression on accelerating the progression of DLD1 cells were suppressed by the upregulation of miR-134 (Figure 6B-D). Furthermore, RT-qPCR showed that knockdown of LINC01278 downregulated the expression of KDM2A, whereas the suppressive effect was abolished by miR-134 inhibition (Figure 6E). In addition, LINC01278 expression was positively correlated with KDM2A in CRC tissues (Figure 6F). To sum up, these results indicated that LINC01278 promoted CRC progression *via* miR-134/KDM2A axis.

Discussion

Multiple lncRNAs have been demonstrated to be involved in the progression of CRC. For instance, Yan et al[17] showed that lncRNA TUG1 sponged miR-138 to accelerate CRC progression through upregulating ZEB2 expression. Huang et al[18] revealed that the upregulation of ST8SIA6-AS1 remarkably facilitated the proliferation of CRC cells *via* the miR-5195/PCBP2 axis. Ni et al[19] showed that lncRNA EGOT knockdown suppressed proliferation and increased apoptosis in CRC through miR-33b-5p/CROT axis. In this study, we found lncRNA LINC01278 was highly expressed in CRC tissues and cell lines, and the silencing of LINC01278 significantly suppressed the progression of CRC cells.

LncRNA could serve as a ceRNA to sponge miRNAs, thus regulating tumor development, including CRC. For example, lncRNA LEF1-AS1 up-regulated DIAPH1 by sponging miR-489 to facilitate the tumorigenesis of CRC[20]. LncRNA TUG1 acted as a ceRNA in regulating KIAA1199 through competitively binding to miR-600 in CRC[21]. LncRNA MIR4435-2HG promoted CRC progression *via* miR-206/YAP1 axis[22]. In our study, we demonstrated that

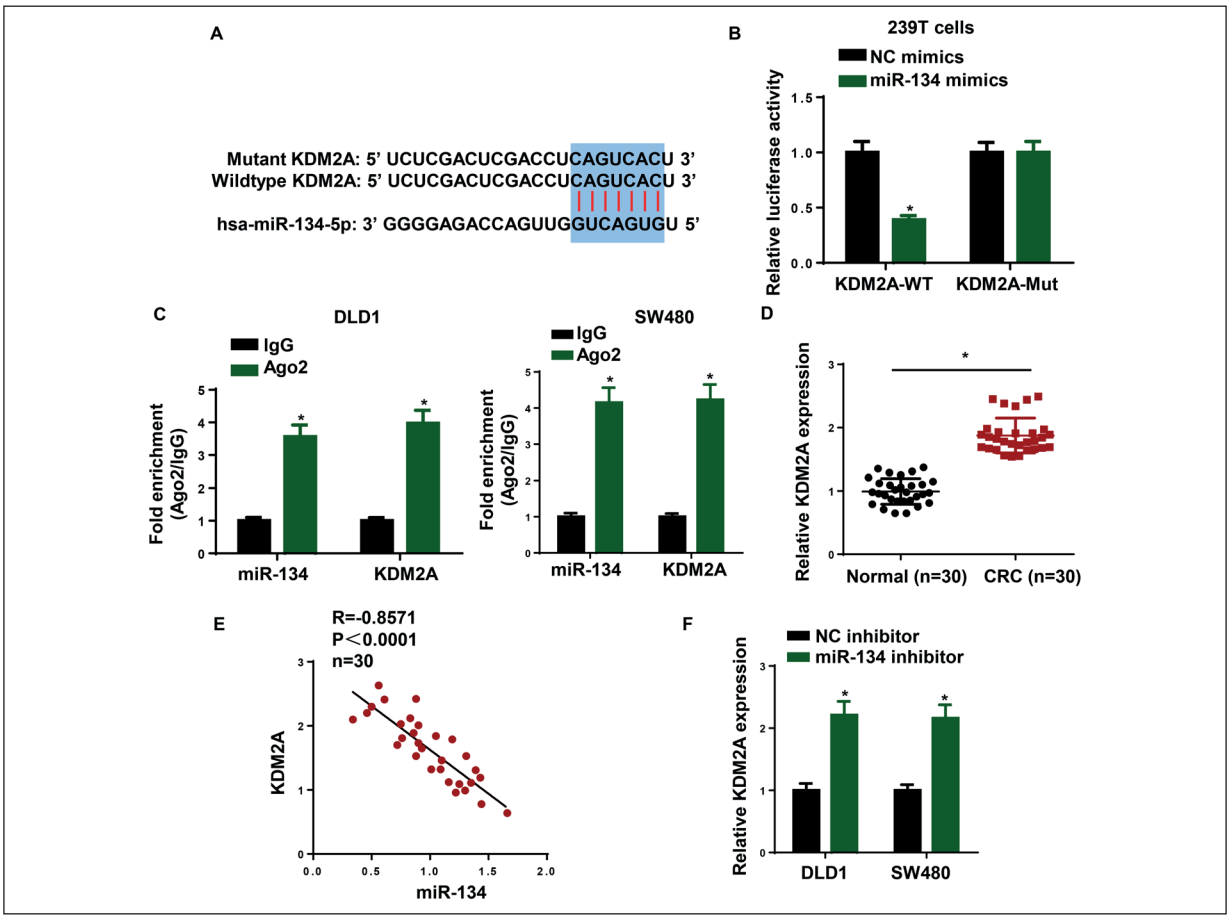

Figure 5. MiR-134 interacted with KDM2A. **A**, The putative binding sites of miR-134 and KDM2A. **B**, The relative Luciferase activity was detected in 293T cells co-transfected with KDM2A-WT or KDM2A-Mut and miR-134 or NC mimics. **C**, The RIP assay was utilized to analyze the interaction between miR-134 and KDM2A. **D**, The expression of KDM2A in CRC tissues and adjacent normal tissues were measured by RT-qPCR. **E**, The correlation between KDM2A and miR-134 expression was evaluated by Pearson's correlation analysis. **F**, The expression of KDM2A was disclosed by RT-qPCR in CRC cells transfected with NC inhibitor and miR-134 inhibitor. The data were presented as mean ± SD (*$p < 0.05$).

LINC01278 directly interacted with miR-134, and LINC01278 silencing suppressed the progression of CRC, while the effects were abolished by miR-134 inhibitor. In addition, miR-134 expression was negatively correlated with LINC01278 expression. In sum, these results indicated that LINC01278 promoted tumorigenesis of CRC through targeting miR-134.

Lysine-specific demethylase 2A (KDM2A), also known as JHDM1A or FBXL11, is a DNA binding protein that binds directly to CpG islands in gene promoters and suppresses the activity of these promoters by removing their H3K36me2 through its N-terminal demethylase JmjC domain[23,24]. KDM2A could act as an oncogenic role in different human malignancies. Wang et al[25] reported that LINC00460 regulated KDM2A to accelerate gastric cancer cell proliferation by sponging miR-342. Ou et al[26] showed that high expression of KDM2A remarkably facilitated tumor growth in cervical cancer. Shou et al[27] showed that miR-3666 inhibited glioblastoma cell growth and migration by sponging KDM2A. However, the function of KDM2A in CRC has not been sufficiently studied. In this study, we showed that KDM2A was a direct target of miR-134, and KDM2A expression was negatively correlated with miR-134 expression. Moreover, KDM2A overexpression promoted the progression of CRC cells, whereas the effects were abolished by the upregulation of miR-134. It was next demonstrated that miR-134 inhibitor reversed the shLINC01278-mediated inhibitory effect on KDM2A expression.

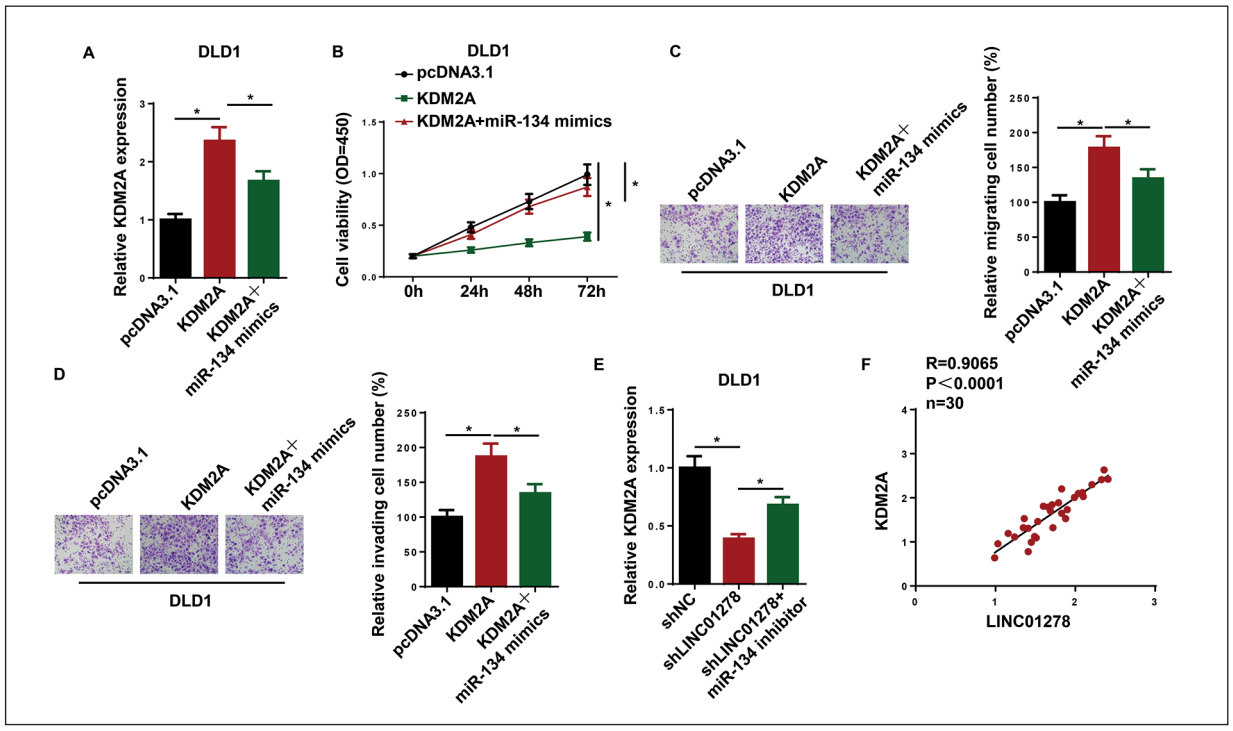

Figure 6. LINC01278 promoted KDM2A expression by acting as a ceRNA of miR-134 in CRC cells. **A**, KDM2A expression in DLD1 cells transfected with pcDNA3.1, KDM2A, KDM2A+miR-134 was detected by RT-qPCR. **B-D**, CCK-8 assay and transwell assay (magnification ×200) were used to assess viability, migration and invasion of DLD1 cells transfected with pcDNA3.1, KDM2A, KDM2A+miR-134 was detected. **E**, KDM2A expression in DLD1 cells transfected with shNC, shLINC01278, shLINC01278+ miR-134 inhibitor was detected by RT-qPCR. **F**, Pearson's correlation analysis was employed to detect the correlation between KDM2A and miR-134 expression in CRC tissues. The data were presented as mean ± SD (*$p < 0.05$).

Conclusions

Our study discovered that LINC01278 upregulated KDM2A expression by sponging miR-134 to promote CRC tumorigenesis. This article presented a new clue to the treatment of CRC and LINC01278 might be a novel molecular target for CRC therapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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