European Review for Medical and Pharmacological Sciences 2020; 24: 2616-2624

Long non-coding RNA MIR4435-2HG recruits miR-802 from FLOT2 to promote melanoma progression

D.-M. MA[1], D. SUN[2], J. WANG[3], D.-H. JIN[1], Y. LI[1], Y.-E. HAN[4]

[1]Department of Dermatology and Venereology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong Province, China
[2]Quality Control Department, Yantai Central Blood Station, Yantai, Shandong Province, China
[3]Department of Outpatient, Qingdao Central Hospital, Qingdao University, Qingdao, Shandong Province, China
[4]Department of Otolaryngology Head and Neck Surgery, Qilu Hospital of Shandong University (Qingdao), Qingdao, Shandong Province, China

Abstract. – OBJECTIVE: The regulatory mechanism of lncRNA MIR4435-2HG has been extensively investigated in human cancers other than melanoma. This study aims to elucidate the role of lncRNA MIR4435-2HG in melanoma.

MATERIAL AND METHODS: The mRNA expression was detected by RT-qPCR. MTT assay, Transwell assay and Dual-Luciferase reporter assay were used to investigate the regulatory mechanism of lncRNA MIR4435-2HG.

RESULTS: Upregulation of lncRNA MIR4435-2HG was identified in melanoma and promoted melanoma cell proliferation, migration and invasion. In addition, lncRNA MIR4435-2HG serves as the ceRNA of miR-802. MiR-802 inhibited melanoma progression by downregulating lncRNA MIR4435-2HG. Besides, miR-802 directly targets FLOT2. And knockdown of FLOT2 restrained the progression of melanoma by downregulating lncRNA MIR4435-2HG and upregulating miR-802.

CONCLUSIONS: LncRNA MIR4435-2HG promotes cell proliferation, migration and invasion in melanoma by sponging miR-802 and upregulating FLOT2.

Key Words:
MIR4435-2HG, Melanoma, miR-802, FLOT2.

Introduction

Melanoma is a common skin tumor caused by excessive proliferation of abnormal melanocytes. Melanoma accounts for a large proportion of skin tumor deaths, is extremely malignant and is prone to metastasis[1]. Although China is a low incidence area of melanoma, its incidence has been increasing in recent years. In addition, the clinical stage of melanoma patients is significantly associated with prognosis. The 5-year survival rates of stage I, II, III and IV were 94%, 44%, 38%, and 4.6%, respectively[2]. Meanwhile, the primary tumor thickness of patients with melanoma was also significantly associated with the prognosis. The 5-year survival rates of ≤1 mm and >4 mm were 92% and 43%[3], respectively. Therefore, early diagnosis and treatment are particularly important for patients with melanoma.

Long non-coding RNAs (lncRNAs) have been widely considered to play important roles in tumorigenesis, including melanoma. LncRNA TUG1 promoted tumor growth and metastasis in malignant melanoma[4]. In addition, Linc00961 has been found to inhibit the proliferation and invasion of cutaneous melanoma cells[5]. The role of lncRNA MIR4435-2HG has been investigated in many human cancers. In particular, lncRNA MIR4435-2HG was upregulated in hepatocellular carcinoma and promoted cancer cell proliferation by upregulating miRNA-487a[6]. But lncRNA MIR4435-2HG was found to be downregulated in osteoarthritis[7]. These findings indicate that MIR4435-2HG is expressed differently in human diseases. Furthermore, the role of MIR4435-2HG in melanoma remains unknown. Therefore, this study aims to explain the regulatory mechanism of MIR4435-2HG in melanoma.

In addition, starBase version 2.0 (http://starbase.sysu.edu.cn/) predicts that MIR4435-2HG has a binding site to miR-802. The abnormal expression of miR-802 has been found in some malignancies.

Corresponding Author: Yu'e Han, MD; e-mail: gongicdnxm265@163.com

It has been reported that miR-802 was upregulated in hepatocellular carcinoma and was associated with poor prognosis[8]. However, miR-802 expression was reduced in gastric cancer. The upregulation of miR-802 suppressed the carcinogenicity of gastric cancer *via* targeting RAB23[9]. This indicates that miR-802 expression has tissue specificity. In addition, lncRNA MIR155HG has been found to promote pancreatic cancer progression through the negative regulation of miR-802[10]. However, the interaction between MIR4435-2HG and miR-802 still needs to be elucidated in melanoma.

Further, we found that flotillin-2 (FLOT2) is a potential target for miR-802. The specific role of FLOT2 in human cancers has been identified. For example, FLOT2 was upregulated and promoted cell metastasis in nasopharyngeal carcinoma[11]. FLOT2 was a target of miR-449 and acted as a prognostic biomarker in glioma[12]. More importantly, miR-802 has been shown to inhibit cell metastasis in prostate cancer by targeting FLOT2[13]. In addition, FLOT2 has been identified as a novel target for miR-34a and is involved in the progression of melanoma[14]. However, it is unclear how MIR4435-2HG regulates miR-802/FLOT2 axis. Therefore, the regulatory mechanism of MIR4435-2HG/miR-802/FLOT2 was investigated in melanoma. At the same time, the roles of MIR4435-2HG, miR-802 and FLOT2 were also confirmed in melanoma. This study may help understand the pathogenesis of melanoma.

Patients and methods

Clinical Specimens

The study was approved by the Institutional Ethics Committee of Qilu Hospital of Shandong University (Qingdao). Written informed consents were obtained from 28 patients with melanoma. All patients were not treated before surgery. The research protocol complies with the principles outlined in the Declaration of Helsinki. Human tissues were frozen in liquid nitrogen and then stored in a refrigerator at -80°C for further experiments.

Cell Culture

Human epidermal HEMa-LP melanocytes and melanoma cell lines A375 and A2058 were purchased from Shanghai GeneChem Co., Ltd. A375 and A2058 cells were seeded in Dulbecco's modified Eagle's medium (DMEM), Invitrogen, Carlsbad, CA, USA) with 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA). HEMa-LP cells were cultured in Invitrogen® Medium 254 (Thermo Fisher Scientific, Inc., St. Louis, MO, USA) supplemented with human melanocyte growth supplement (Thermo Fisher Scientific, Inc., St. Louis, MO, USA). Finally, they were incubated in a humid atmosphere at 37°C with 5% CO_2.

Cell Transfection

Lentivirus vectors overexpressing MIR4435-2HG, MIR4435-2HG siRNA, miR-802 mimics, miR-802 inhibitor, FLOT2 siRNA were purchased from GeneChem (Shanghai, China). Next, they were transfected into A375 cells using Lipofectamine 2000 (Invitrogen/Thermo Fisher Scientifc, Inc., Waltham, MA, USA), respectively.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used to extract total RNA from melanoma tissues and cells. A cDNA solution was synthesized using a PrimeScript RT reagent kit (TaKaRa, Dalian, China). Quantitative RT-PCR was performed using the SYBR-Green RT-PCR kit (TaKaRa, Dalian, China) on ABI7500 Fast Real-time PCR System (Applied Biosystems, Thermo Fisher Scientifc, Inc., Waltham, MA, USA). U6 and glyceraldehyde phosphate dehydrogenase (GAPDH) were used as internal references. The primers used were: MIR4435-2HG forward 5-GAC ATT CCA GAC AAG CGG TG-3′; reverse 5-TCC ACT TTG CTT GTC AGG GA-3′; miR-802 forward: 5-CGT TGT GTA GCT TAT CAG ACT G-3′and reverse, 5-AAT GGT TGT TCT CCA CAC TCT C-3′; U6-forward: 5-GCT TCG GCA GCA CAT ATA CTA AAA T-3′ and reverse, 5-CGC TTC ACG AAT TTG CGT GTC AT-3′; FLOT2 forward: 5-CCC CAG ATT GCT GCC AAA-3′and reverse, 5-TCC ACT GAG GAC CAC AAT CTC A-3; GAPDH forward: 5-ACA ACT TTG GTA TCG TGG AAG G-3′, and reverse, 5-GCC ATC ACG CCA CAG TTT C-3′.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay

MTT assay was used to measure cell proliferation. A375 cells were seeded in 96-well plates. The transfected cells were incubated for 24, 48, 72, and 96 h, respectively. These cells were then incubated with MTT solution (5 mg/ml; Sigma-Aldrich, Merck KGaA, Darmstadt, Germany) for 4 h at 37˚C. The absorbance at 490 nm was

measured using a spectrophotometer (Perkin-Elmer, Inc., Waltham, MA, USA).

Transwell Assay

Cell invasion was detected in the upper chamber with Matrigel (BD Biosciences, San Jose, CA, USA). Cell migration was measured without Matrigel. First, A375 cells (4×10^3 cells/well) were seeded into the upper chambers (8 μm pore size; Corning Incorporated, Corning, NY, USA). DMEM medium with 10% FBS was placed in the lower chamber. Next, these cells were incubated with 5% CO_2 at 37˚C for 24 h. Finally, the moving cells on the lower surface were fixed and stained for 30 mins, and then counted with a light microscope.

Dual-Luciferase Reporter Assay

The pGL3 plasmids (Promega Corporation, Madison, WI, USA) with miR-802 mimics and wt-MIR4435-2HG or mut-MIR4435-2HG were transfected into A375 cells to verify the binding of MIR4435-2HG and miR-802. After 48 h of incubation, luciferase activity was determined by dual-luciferase reporter assay system (Promega Corporation, Madison, WI, USA). The relationship between FLOT2 and miR-802 was also investigated according to the above experimental procedure.

Statistical Analysis

Data are shown as mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism 6.0 (La Jolla, CA, USA) and Statistical Product and Service Solutions (SPSS) 17.0 (IBM Corp., Armonk, NY, USA). Differences between groups were calculated using Student's *t*-test or One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. It is defined as statistically significant at $p<0.05$.

Results

LncRNA MIR4435-2HG Promotes Cell Proliferation, Migration and Invasion in Melanoma

The expression of MIR4435-2HG was detected in melanoma tissues. RT-qPCR showed that MIR4435-2HG expression was increased in melanoma tissues compared to normal tissues (Figure 1A). In addition, compared to HEMa-LP melanocytes, upregulation of MIR4435-2HG was detected in A375 and A2058 melanoma cells (Figure 1B). The alternation of MIR4435-2HG expression was more pronounced in A375 than in A2058 cells. Therefore, A375 cells were used to explore the role of MIR4435-2HG in melanoma cells. Next, MIR4435-2HG siRNA was transfected into A375 cells. We found that MIR4435-2HG expression was significantly reduced by its siRNA in A375 cells (Figure 1C). Functionally, knockdown of MIR4435-2HG restrained A375 cell proliferation (Figure 1D). Meanwhile, cell migration and invasion were suppressed by MIR4435-2HG siRNA (Figure 1E, 1F). Collectively, lncRNA MIR4435-2HG is involved in the progression of melanoma by acting as an oncogene.

LncRNA MIR4435-2HG serves as a ceRNA for miR-802

Next, starBase version 2.0 (http://starbase.sysu.edu.cn/) predicts that MIR4435-2HG has a binding site to miR-802 (Figure 2A). The dual luciferase reporter assay showed that miR-802 mimics reduced the luciferase activity of wt-MIR4435-2HG in A375 cells (Figure 2B). Next, miR-802 expression was measured in melanoma tissues. Compared to normal tissues, downregulation of miR-802 was found in melanoma tissues (Figure 2C). In addition, MIR4435-2HG expression was found to be inversely correlated with miR-802 expression in melanoma tissues (Figure 2D). And it was found that miR-802 expression was reduced by upregulation of MIR4435-2HG and increased by downregulation of MIR4435-2HG (Figure 2E). At the same time, miR-802 mimics inhibited the expression of MIR4435-2HG, while miR-802 inhibitor promoted MIR4435-2HG expression in A375 cells (Figure 2F). These results reveal that lncRNA MIR4435-2HG acts as a molecular sponge for miR-802.

MiR-802 Regulates Melanoma Progression by Mediating LncRNA MIR4435-2HG

MiR-802 expression was observed in melanoma cells. Compared to HEMa-LP cells, downregulation of miR-802 was identified in A375 and A2058 melanoma cells (Figure 3A). Next, miR-802 mimics and MIR4435-2HG vector were transfected into A375 cells. We found that miR-802 mimics enhanced its expression in A375 cells. After the MIR4435-2HG vector was transfected, the increased expression of miR-802 was recovered (Figure 3B). Functionally, cell proliferation, migration and invasion were inhibited by miR-802 overexpression. In addition, the upregulation of MIR4435-2HG attenuated the inhibitory effects of miR-802 on cell proliferation, migration

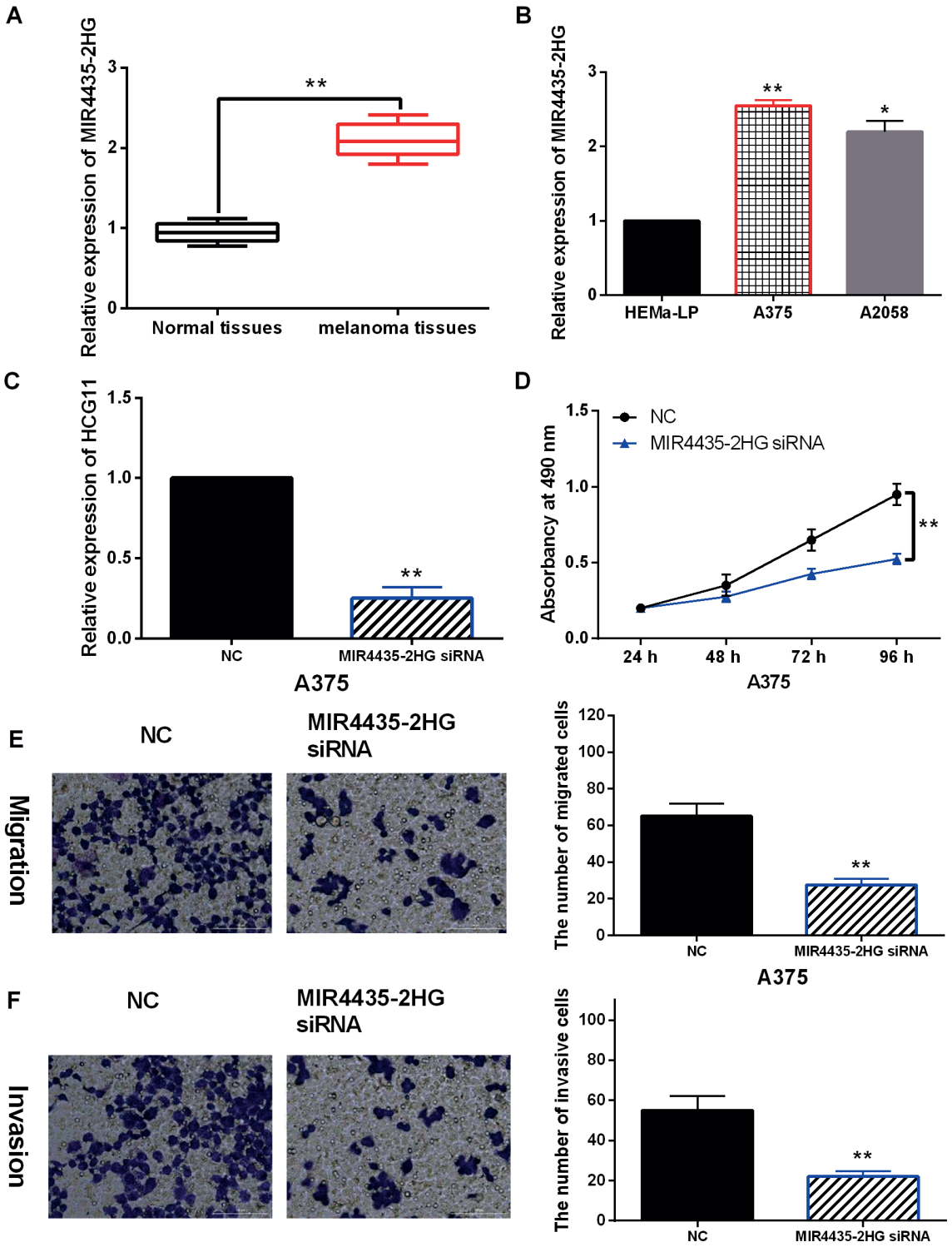

Figure 1. LncRNA MIR4435-2HG promotes cell proliferation, migration and invasion in melanoma. (**A-B**) The expression of MIR4435-2HG in melanoma tissues and cells (**C**) MIR4435-2HG expression in A375 cells with its siRNA. (**D-F**) Cell proliferation, migration and invasion in A375 cells with MIR4435-2HG siRNA (magnification, x200) *$p < 0.05$, ** $p < 0.01$

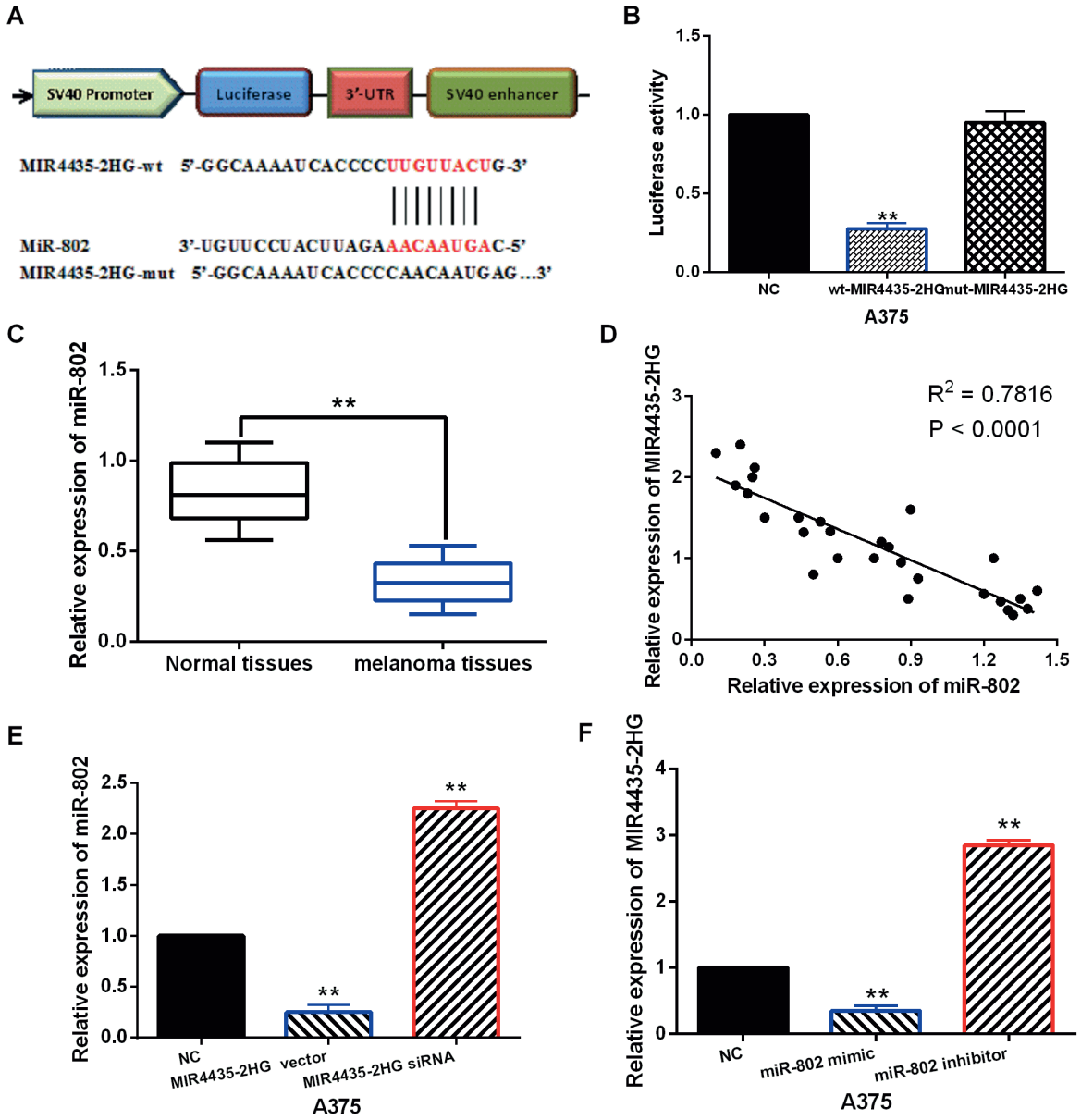

Figure 2. LncRNA MIR4435-2HG acts as a molecular sponge of miR-802. (**A**) The binding sites between MIR4435-2HG with miR-802. (**B**) Luciferase reporter assay (**C**) MiR-802 expression in melanoma tissues (**D**) A negative correlation between MIR4435-2HG and miR-802 expression in melanoma tissues (**E**) MiR-802 expression regulated by MIR4435-2HG siRNA and vector (**F**) MIR4435-2HG expression in A375 cells containing miR-802 mimics or inhibitor $^{**}p < 0.01$.

and invasion in A375 cells (Figure 3C, 3D, 3E). The results imply that miR-802 restrains cell proliferation, migration and invasion in melanoma by inhibiting MIR4435-2HG expression.

MiR-802 Directly Targets FLOT2

Further, miR-802 is predicted to have a binding site to the 3'-UTR of FLOT2 in the TargetScan database (http://www.targetscan.org, Figure 4A). We found that miR-802 mimics reduced the luciferase activity of wt-FLOT2, but had little effect on that of mut-FLOT2 (Figure 4B). Next, FLOT2 expression was assessed in melanoma tissues. Upregulation of FLOT2 was found in melanoma tissues compared to normal tissues (Figure 4C). And miR-802 expression

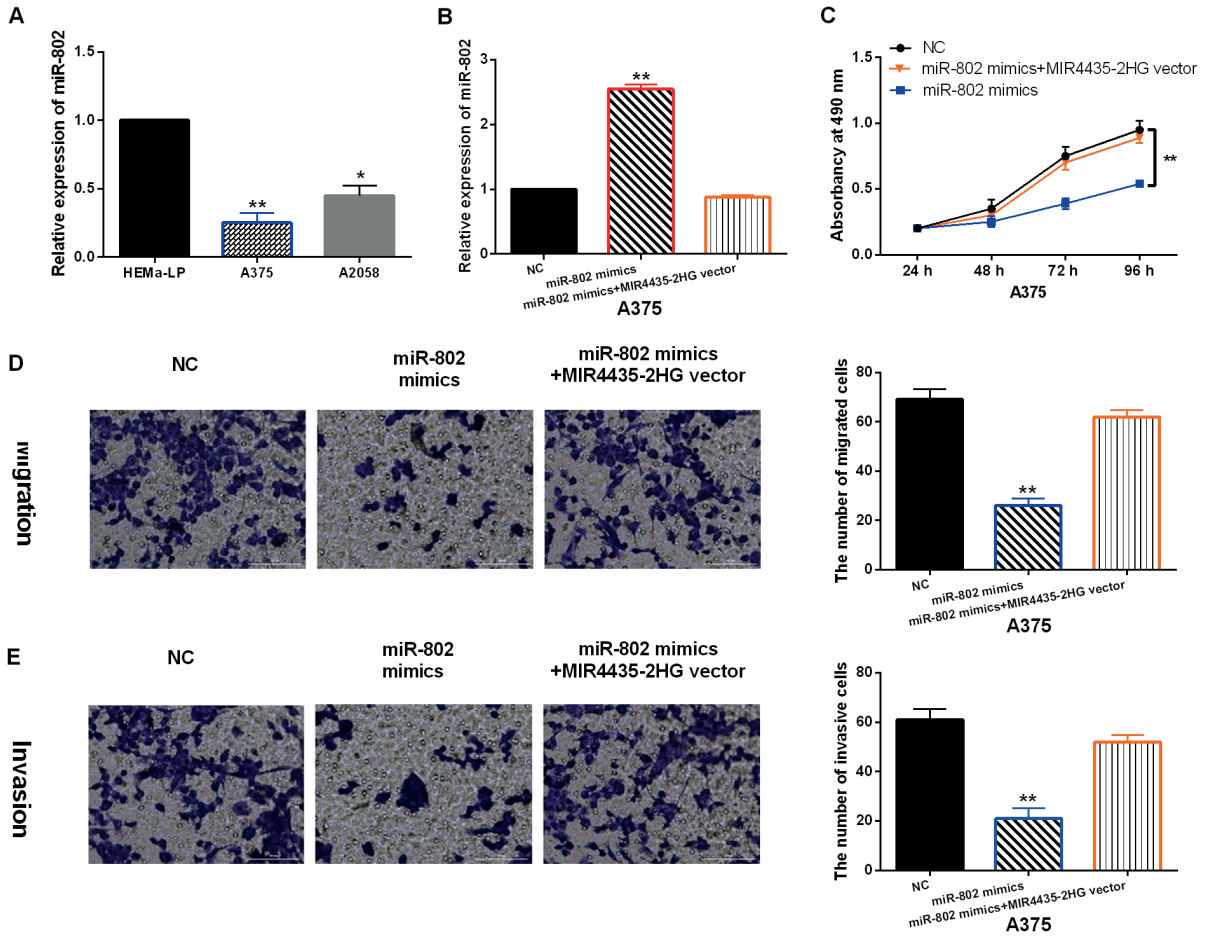

Figure 3. MiR-802 regulates melanoma progression by mediating lncRNA MIR4435-2HG. (**A**) The expression of miR-802 in A375, A2058, and HEMa-LP cells. (**B**) MiR-802 expression in A375 cells with miR-802 mimics, or miR-802 mimics+ MIR4435-2HG siRNA. (**C-E**) Cell proliferation, migration and invasion in A375 cells with miR-802 mimics, or miR-802 mimics+ MIR4435-2HG siRNA (magnification, x200) $^{**}p < 0.05$, $^{**}p < 0.01$

was found to negatively regulate FLOT2 expression in melanoma tissues (Figure 4D). In contrast, a positive correlation was detected between MIR4435-2HG and FLOT2 expression in melanoma tissues (Figure 4E). At the same time, overexpression of miR-802 reduced FLOT2 expression, while downregulation of miR-802 promoted FLOT2 expression in A375 cells (Figure 4F). However, FLOT2 expression was increased by upregulation of MIR4435-2HG and decreased by downregulation of MIR4435-2HG (Figure 4G). Therefore, we consider that miR-802 directly targets FLOT2. And MIR4435-2HG can upregulate FLOT2 expression by sponging miR-802 in melanoma.

FLOT2 Regulates Melanoma Progression by Mediating LncRNA MIR4435-2HG/miR-802 Axis

Similarly, FLOT2 expression in A375 and A2058 melanoma cells was also higher than HEMa-LP cells (Figure 5A). Next, the MIR4435-2HG vector or miR-802 inhibitor was transfected into A375 cells with FLOT2 siRNA to explore their interactions. RT-qPCR showed that FLOT2 siRNA significantly reduced its expression in A375 cells. However, MIR4435-2HG vector or miR-802 inhibitor restored the decreased expression of FLOT2 (Figure 5B). Functionally, knockdown of FLOT2 restrained cell proliferation, migration and invasion in A375

cells. Additionally, upregulation of MIR4435-2HG or downregulation of miR-802 eliminated the inhibitory effects of FLOT2 siRNA on A375 cell proliferation, migration and invasion (Figure 5C, 5D, 5E). In summary, FLOT2 regulates the progression of melanoma by mediating the lncRNA MIR4435-2HG/miR-802 axis.

Discussion

In our study, upregulation of MIR4435-2HG was detected in melanoma. Functionally, knockdown of MIR4435-2HG restrained the proliferation, migration and invasion of melanoma cells. Increased MIR4435-2HG expression was also found in colorectal and ovarian cancers[15,16]. Moreover, MIR4435-2HG plays a carcinogenic role in lung and gastric cancers[17,18]. These findings are consistent with our results. These results indicate that MIR4435-2HG acts as an oncogene in melanoma. In addition, we found that lncRNA MIR4435-2HG acts as a molecular sponge for miR-802. Furthermore, MIR4435-2HG is involved in the progression of melanoma by interacting with miR-802.

Previous studies have shown that miR-802 was downregulated in prostate and cervical cancers[13,19]. Downregulation of miR-802 was also detected in melanoma. And miR-802 overexpression suppressed the proliferation, migration and invasion of melanoma cells. Consistent with our results, miR-802 has been reported to inhibit cell viability and invasion in tongue squamous cell carcinoma[20]. Additionally, it has been reported that the lncNRA MIR155HG/miR-802 axis promoted the tumorigenesis of pancreatic cancer[10]. Here, lncRNA MIR4435-2HG also promotes the

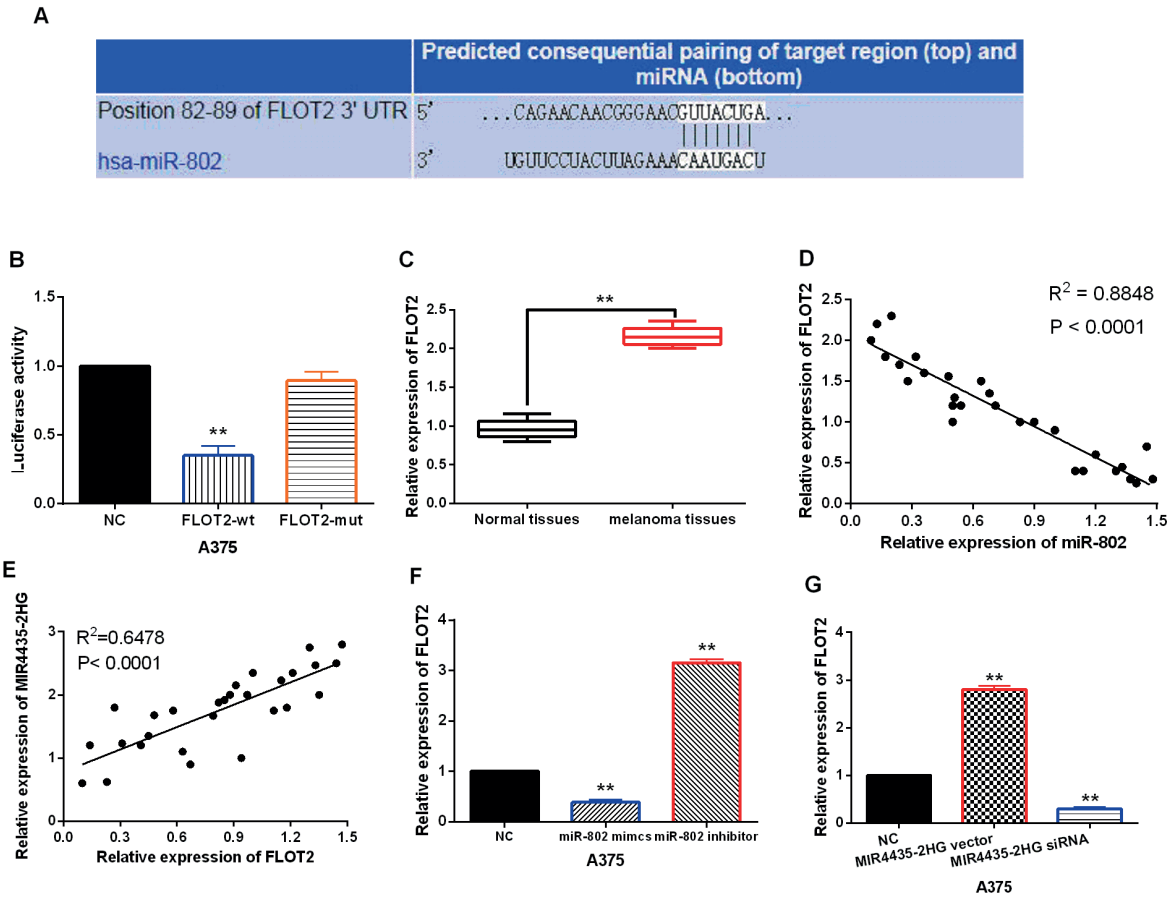

Figure 4. MiR-802 directly targets FLOT2. (**A**) The binding sites between miR-802 and FLOT2. (**B**) Luciferase reporter assay (**C**) FLOT2 expression in melanoma tissues (**D**) A negative correlation between FLOT2 and miR-802 expression in melanoma tissues (**E**) A positive correlation between MIR4435-2HG and FLOT2 expression in melanoma tissues (**F**) FLOT2 expression in A375 cells with miR-802 mimics or inhibitor (**G**) FLOT2 expression in AGS cells with MIR4435-2HG siRNA or vector ** p <0.01.

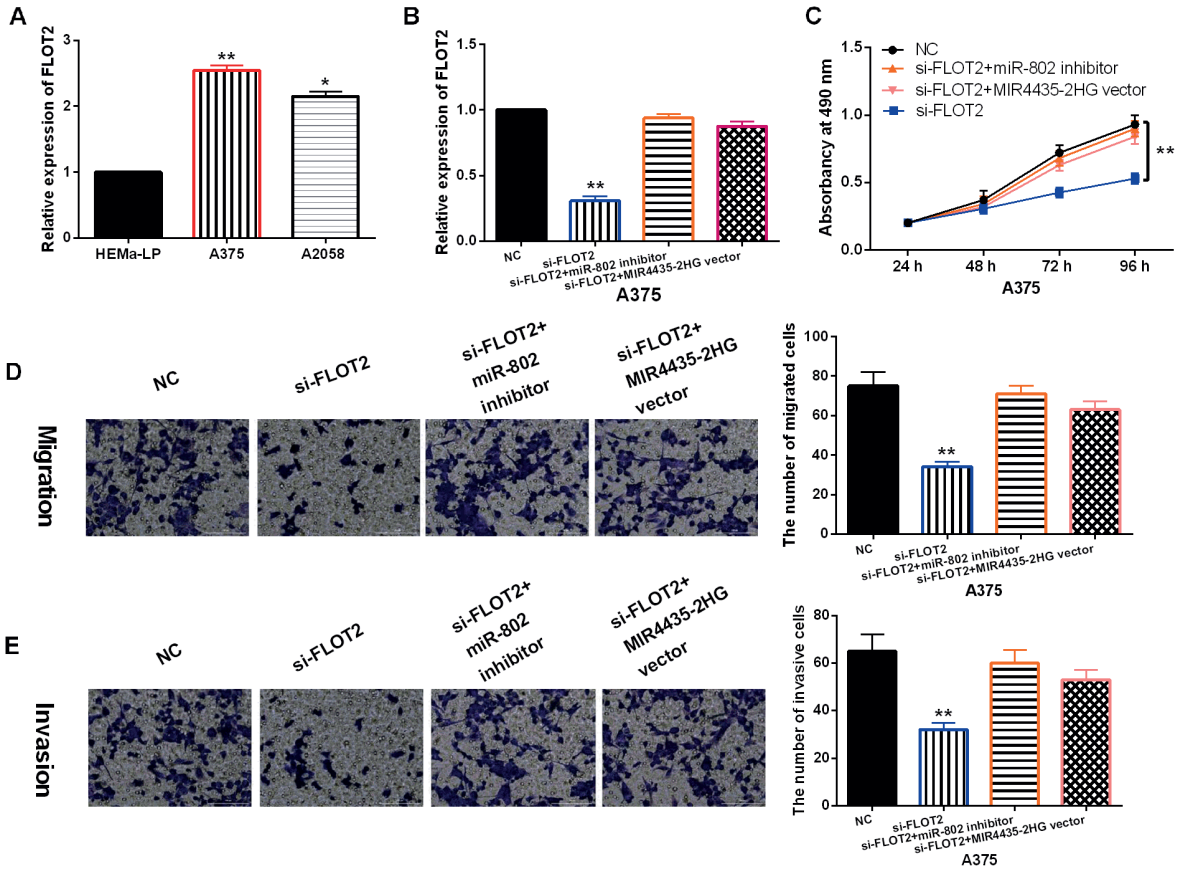

Figure 5. FLOT2 regulates melanoma progression by mediating lncRNA MIR4435-2HG/miR-802 axis. (**A**) The expression of FLOT2 in A375, A2058 and HEMa-LP cells (**B**) FLOT2 expression in A375 cells with FLOT2 siRNA, FLOT2 siRNA+miR-802 inhibitor or FLOT2 siRNA+ MIR4435-2HG vector. (**C-E**) Cell proliferation, migration and invasion in A375 cells with FLOT2 siRNA, FLOT2 siRNA+miR-802 inhibitor or FLOT2 siRNA+ MIR4435-2HG vector (magnification, x200) **p* <0.05, ** *p* <0.01.

progression of melanoma by acting as a ceRNA of miR-802, which has not been reported in previous studies. It is well known that miRNAs regulate tumorigenesis by binding to target genes including miR-802. Specifically, miR-802 inhibited breast cancer proliferation by targeting FoxM1[21]. In this study, miR-802 was found to directly target FLOT2 in melanoma.

Here, upregulation of FLOT2 was found in melanoma. Knockdown of FLOT2 restrained the proliferation, migration and invasion of melanoma cells. Increased FLOT2 expression and its inhibitory effects have also been found in gastric cancer and lung adenocarcinoma[22,23]. In addition, a negative correlation between miR-802 and FLOT2 expression was identified in melanoma. Furthermore, miR-802 can attenuate the carcinogenic effect of FLOT2 in melanoma. This also indicates that miR-802 inhibits melanoma progression by downregulating FLOT2. The same results have been observed by Wang et al[13]. Besides that, a positive correlation was found between lncRNA MIR4435-2HG and FLOT2 in melanoma. Because MIR4435-2HG can sponge miR-802 that targets FLOT2, lncRNA MIR4435-2HG and FLOT2 expressions are upregulated and miR-802 is downregulated in melanoma. Functionally, the upregulation of MIR4435-2HG impaired the inhibitory effect of FLOT2 siRNA in melanoma. The results show that lncRNA MIR4435-2HG promotes the tumorigenesis of melanoma by upregulating FLOT2.

Conclusion

In summary, lncRNA MIR4435-2HG is upregulated and functions as an oncogene in melanoma. Specifically, lncRNA MIR4435-2HG promotes cell proliferation, migration and invasion in mel-

anoma by competitively binding to miR-802 and upregulating FLOT2. Our research indicates that the lncRNA MIR4435-2HG/miR-802/ FLOT2 axis may be a breakthrough for melanoma treatment.

Funding

This study is supported by Natural Science Foundation of China (81700467) and the Key Research and Development Plan of Shandong Province (2016GSF201212 and 2015GSF118171).

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Rozeman EA, Dekker TJA, Haanen JBAG, Blank CU. Advanced melanoma: current treatment options, biomarkers, and future perspectives. Am J Clin Dermatol 2018; 19: 303-317.
2) Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe - a systematic review of the literature. Clin Epidemiol 2016; 8: 109-122.
3) Padrik P, Valter A, Valter E, Baburin A, Innos K. Trends in incidence and survival of cutaneous malignant melanoma in Estonia: a population-based study. Acta Oncol 2017; 56: 52-58.
4) Long J, Menggen Q, Wuren Q, Shi Q, Pi X. Long noncoding RNA taurine-upregulated gene1 (TUG1) promotes tumor growth and metastasis through TUG1/Mir-129-5p/Astrocyte-elevated gene-1 (AEG-1) axis in malignant melanoma. Med Sci Monit 2018; 24: 1547-1559.
5) Mu X, Mou KH, Ge R, Han D, Zhou Y, Wang LJ. Linc00961 inhibits the proliferation and invasion of skin melanoma by targeting the miR367/PTEN axis. Int J Oncol 2019; 55: 708-720.
6) Kong Q, Liang C, Jin Y, Pan Y, Tong D, Kong Q, Zhou J. The lncRNA MIR4435-2HG is upregulated in hepatocellular carcinoma and promotes cancer cell proliferation by upregulating miRNA-487a. Cell Mol Biol Lett 2019; 24: 26.
7) Xiao Y, Bao Y, Tang L, Wang L. LncRNA MIR4435-2HG is downregulated in osteoarthritis and regulates chondrocyte cell proliferation and apoptosis. J Orthop Surg Res 2019; 14: 247.
8) Jiang C, Liu X, Wang M, Lv G, Wang G. High blood miR-802 is associated with poor prognosis in HCC patients by regulating DNA damage response 1 (REDD1)-mediated function of T cells. Oncol Res 2019; 27: 1025-1034.
9) Zhang XY, Mu JH, Liu LY, Zhang HZ. Upregulation of miR-802 suppresses gastric cancer oncogenicity via targeting RAB23 expression. Eur Rev Med Pharmacol Sci 2017; 21: 4071-4078.
10) Qin Y, Liu X, Pan L, Zhou R, Zhang X. Long noncoding RNA MIR155HG facilitates pancreatic cancer progression through negative regulation of miR-802. J Cell Biochem 2019; 120: 17926-17934.
11) Zhao L, Lin L, Pan C, Shi M, Liao Y, Bin J, Liao W. Flotillin-2 promotes nasopharyngeal carcinoma metastasis and is necessary for the epithelial-mesenchymal transition induced by transforming growth factor-beta. Oncotarget 2015; 6: 9781-9793.
12) Huang S, Zheng S, Huang S, Cheng H, Lin Y, Wen Y, Lin W. Flot2 targeted by miR-449 acts as a prognostic biomarker in glioma. Artif Cells Nanomed Biotechnol 2019; 47: 250-255.
13) Wang D, Lu G, Shao Y, Xu D. microRNA-802 inhibits epithelial-mesenchymal transition through targeting flotillin-2 in human prostate cancer. Biosci Rep 2017; 37.
14) Liu R, Xie H, Luo C, Chen Z, Zhou X, Xia K, Chen X, Zhou M, Cao P, Cao K, Zhou J. Identification of FLOT2 as a novel target for microRNA-34a in melanoma. J Cancer Res Clin Oncol 2015; 141: 993-1006.
15) Ouyang W, Ren L, Liu G, Chi X, Wei H. LncRNA MIR4435-2HG predicts poor prognosis in patients with colorectal cancer. PeerJ 2019; 7: e6683.
16) Gong J, Xu X, Zhang X, Zhou Y. LncRNA MIR4435-2HG is a potential early diagnostic marker for ovarian carcinoma. Acta Biochim Biophys Sin (Shanghai) 2019; 51: 953-959.
17) Qian H, Chen L, Huang J, Wang X, Ma S, Cui F, Luo L, Ling L, Luo K, Zheng G. The lncRNA MIR4435-2HG promotes lung cancer progression by activating beta-catenin signalling. J Mol Med (Berl) 2018; 96: 753-764.
18) Wang H, Wu M, Lu Y, He K, Cai X, Yu X, Lu J, Teng L. LncRNA MIR4435-2HG targets desmoplakin and promotes growth and metastasis of gastric cancer by activating Wnt/beta-catenin signaling. Aging (Albany NY) 2019; 11: 6657-6673.
19) Zhang Q, Lv R, Guo W, Li X. microRNA-802 inhibits cell proliferation and induces apoptosis in human cervical cancer by targeting serine/arginine-rich splicing factor 9. J Cell Biochem 2019; 120: 10370-10379.
20) Wu X, Gong Z, Sun L, Ma L, Wang Q. MicroRNA-802 plays a tumour suppressive role in tongue squamous cell carcinoma through directly targeting MAP2K4. Cell Prolif 2017; 50.
21) Yuan F, Wang W. MicroRNA-802 suppresses breast cancer proliferation through downregulation of FoxM1. Mol Med Rep 2015; 12: 4647-4651.
22) Li Q, Peng J, Li X, Leng A, Liu T. miR-449a targets Flot2 and inhibits gastric cancer invasion by inhibiting TGF-beta-mediated EMT. Diagn Pathol 2015; 10: 202.
23) Wei G, Xu Y, Peng T, Yan J. miR-133 involves in lung adenocarcinoma cell metastasis by targeting FLOT2. Artif Cells Nanomed Biotechnol 2018; 46: 224-230.