MicroRNA-128 suppresses cell growth and metastasis in colorectal carcinoma by targeting IRS1

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Abstract. Evidence has shown that microRNAs play important roles in tumor development, progression, and metastasis. miR-128 has been reported to be deregulated in different tumor types, whereas the function of miR-128 in colorectal carcinoma (CRC) largely remains to be elucidated. The aim of the present study was to investigate the clinical significance, biological effects and underlying mechanisms of miR-128 in CRC using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blotting. It was found that the expression of miR-128 was downregulated in CRC tissues and cell lines as determined by RT-qPCR. Furthermore, the expression of miR-128 in tumor tissues was significantly negatively correlated with TNM stage and lymph node metastasis in CRC patients. Functional assay revealed that the overexpression of miR-128 inhibited CRC cell proliferation, colony formation, migration and invasion and promoted apoptosis in vitro, and suppressed CRC xenograft tumor growth in vivo. In addition, insulin receptor substrate 1 (IRS1), a key mediator in oncogenic insulin-like growth factor (IGF) signaling, was confirmed as a direct target of miR-128 by a luciferase reporter assay. Western blot analysis indicated that the overexpression of miR-128 significantly downregulated IRS1 expression and its downstream Akt signaling in CRC cells. Moreover, miR-128 was negatively associated with IRS1 in CRC tissues compared to adjacent non-tumor tissues. Taken together, these data suggested that miR-128 serves as a tumor suppressor and blocks CRC growth and metastasis by targeting IRS1.

Introduction

Colorectal cancer has the third highest incidence of human malignant diseases and is the fourth most common cause of cancer-associated mortality (1). Over one million new cases are detected annually according to the International Agency for Research on Cancer (2). Colorectal cancer is caused by the accumulation of mutations in numerous genes, including alterations in oncogenes and tumor-suppressor genes, which lead to the activation of oncogenes and the inactivation of tumor-suppressor genes (3). Although previous studies have focused on the biological mechanism of colorectal carcinoma (CRC) and a series of tumor-suppressor genes and oncogenes have been identified in recent years, the pathological process and underlying mechanism of CRC remains to be elucidated. Therefore, identification of the molecular mechanisms by which CRC initiates, progresses, invades and recurs is imperative in order to develop novel and effective therapeutic strategies.

MicroRNAs (miRNAs) are a large family of endogenous small non-coding RNAs (19-24 nt) that play important regulatory roles in animals and plants by binding to the 3' untranslated regions (3'UTRs) of target mRNAs, resulting in blocking of translation and/or mRNA degradation (4-6). Accumulating evidence has shown that miRNAs play diverse roles in the regulation of tumor proliferation, invasion, apoptosis and therapy resistance, and act as oncogenes or tumor suppressors depending on the target mRNAs (7-9). Findings have shown that some miRNAs are involved in CRC development, progression and metastasis through the regulation of different cell processes, including apoptosis, migration or invasion (10-12). Thus, miRNAs are presently considered potential novel targets for CRC therapy.

miR-128, an important miRNA, has been shown to be downregulated in several types of cancer including prostate cancer, glioma, head and neck squamous cell carcinoma (HNSCC), and non-small cell lung cancer, and to inhibit cancer cell growth and invasion when overexpressed (13-15). Concerning CRC, there is currently only one study showing that miR-128 expression was significantly associated with a poorer recurrence rate, and that miR-128 directly targeted NEK2, induced G2-phase cell cycle arrest, and inhibited cancer cell proliferation in CRC cells (16). However, the function of miR-128 on CRC cell apoptosis, migration, invasion and the underlying molecular mechanisms remain relatively unclear. The present study was therefore undertaken to evaluate the potential role of miR-218 in CRC cells.
In the present study, we identified that miR-128 was downregulated in CRC tissue and cell lines, suppressed cell proliferation, migration and invasion, induced apoptosis in vitro, and inhibited tumor growth in vivo. We also showed the potential tumor suppressor role of miR-128 involved in CRC by identifying the new targeting gene IRS1. Furthermore, we showed that miR-128 directly targets the 3'UTR of IRS1 to regulate its expression and downstream signaling proteins. Our data suggest a new perspective on how miR-128 is involved in CRC.

Materials and methods

Human tissue specimens. Forty-five paired CRC and adjacent normal tissues were collected from the First Hospital of Jilin University (Changchun, China). CRC tissues were obtained from patients undergoing resection, and adjacent colon tissues were obtained from the distal normal colon tissue of CRC cancers. None of the patients received chemotherapy or radiotherapy prior to surgery. Tissues were immediately frozen in liquid nitrogen, and stored at -80 °C for subsequent experiments. The patient clinicopathological characteristics were collected and are listed in Table I. Informed consent was obtained from all the patients prior to the study. The study was approved by the Ethics Committee of Jilin University (Changchun, China).

Cell lines and culture. The human LoVo, CaCoS2, SW1116, SW480, and HCT-116 CRC cell lines and a normal colonic cell line (NCM460) were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The cells were incubated in Dulbecco’s modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) (both from Gibco-BRL, Gaithersburg, MD, USA), 100 U/ml penicillin and 100 mg/ml streptomycin at 37 °C in an atmosphere of 5% CO₂.

Reverse transcription-quantitative polymerase chain reaction. Total RNA of tissues and cells were isolated using TRIzol reagent according to the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA). The concentration of all RNAs was measured using a spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA), and 1 µg RNA was used for complementary DNA (cDNA) synthesis using the M-MLV reverse transcriptase kits (Promega, Madison, WI, USA) according to the manufacturer's instructions. qPCR was performed using SYBR Premix Ex Taq (Takara, Dalian, China). The miR-128 mimics (miR-128) and corresponding negative control (miR-NC) were purchased from GenePharma (Shanghai, China). Transfection was performed using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions.

Cell growth and colony formation assays. Transfected (2x10³ cells/well) were plated in 96-well plates and were cultured at the indicated time points (24, 48 and 72 h) when cell growth was estimated by the Cell Counting Kit-8 (CCK-8) (Dojindo, Japan) according to the manufacturer's instructions. For colony formation assay, 1x10³ transfected cells/well were seeded into a 6-well plate and cultured for 14 days. The cells were fixed with 4% paraformaldehyde for 20 min and counted after staining with 1% crystal violet. The percentage colony formation was calculated by the adjusting control (miR-NC or si-NC) to 100%.

Cell apoptotic analysis. Cell apoptotic analysis was performed using the phycocerythrin (PE)-Annexin V apoptosis detection kit (BD Pharmingen, San Jose, CA, USA). Briefly, the cells were seeded in 6-well plates at 4x10⁵ cells/well. Twenty-four hours after transfection, the cells were suspended and those that adhered, were collected and labeled with Annexin V for 15 min in dark place. Propidium iodide (PI) (50 µg/ml) was added to each sample prior to the cell apoptosis. Distribution was analyzed using the FACSCalibur flow cytometer (BD Biosciences, Mansfield, MA, USA).

In addition, the activity of caspase-3 and -8 was detected as an additional indicator of apoptosis using caspases colorimetric protease assay kits (Millipore Corporation, Billerica, MA, USA) according to the manufacturer's instructions.

Wound-healing assay. A wound-healing assay was also performed for analysis of cell migration in vitro. Briefly, SW480 cells were transfected with miR-128 mimics or miR-NC, cultured in 6-well plates (5x10⁵ cells/well) and incubated overnight. An artificial homogenous wound was scratched into the monolayer using a sterile plastic micropipette tip. After wounding, the debris was removed by washing the cells with phosphate-buffered saline (PBS), and complete RPMI-1640 medium with 10% FBS was added. Cell migration towards the wounded area was observed and photographed after 24 h. Wound closure (%) was calculated as the area of migrated cells divided by the wounded area at 0 h. Individual cells were quantified as an average of at least five fields for each experiment.

Cell invasion assay. Cell invasion was performed by Transwell assay (BD Biosciences) according to the manufacturer's instructions. Transfected cells (2x10³) in serum-free medium were added to each upper insert pre-coated with Matrigel matrix. Medium (600 µl) with 10% FBS was added to the lower chamber to serve as a chemoattractant. Forty-eight hours after incubation, the non-invasive cells were removed from the upper surface of the Transwell membrane with a cotton swab, and the invasive cells on the lower membrane surface were fixed in methanol, and stained with 0.2% crystal violet for 10 min. Images of five randomly selected fields of the fixed cells were captured and the cells were counted.
Western blotting. Protein was extracted from cells or tissue using Cell Lysis Buffer (Cell Signaling Technology, Danvers, MA, USA). After centrifugation for 15 min at 4°C at 14,000 g, the supernatant was collected and the concentrations of protein were determined with a bicinchoninic acid protein assay kit (Pierce, Rockford, IL, USA). Proteins (30 µg) were electrophoresed in SDS-polyacrylamide gels (Invitrogen) and transferred to polyvinylidene fluoride membranes (Millipore, Bedford, MA, USA). After blocking with 5% non-fat milk, the membranes were incubated with specific primary antibodies overnight at 4˚C, including anti-IRS1, anti-Bcl-2, anti-MMP-2, anti-cyclinD1, anti-Akt, anti-pAkt and anti-β-actin (all antibodies from Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA; all diluted at 1:1,000). The membranes were washed three times with TBST buffer, incubated with the corresponding horseradish peroxidase (HRP)-conjugated secondary antibody (Santa Cruz Biotechnology, Inc.) for 2 h at room temperature and then exposed to X-ray film (Denville Scientific) using chemiluminescent reagents. β-actin was used as the internal control.

Tumor xenograft treatment model. Animal experimental procedures were approved by the Institutional Animal Care and Use Committee of Jilin University. Twenty 6-week-old male BALB/C nude mice were obtained from the Experimental Animal Center of Changchun Institute for Biological Sciences (Changchun, China). The animals were kept and the experiments were performed in accordance with the European Community guidelines for the use of experimental animals (86/609/EEC).

An equal number of SW480 cells (2x10⁶) stably expressed in miR-128 mimic or miR-NC were suspended in 100 µl serum-free RPMI-1640 medium and injected subcutaneously into the right rear flank of each mouse (n=10) to establish a CRC xenograft model. Tumor volumes were measured every 7 days using calipers along the two major axes after treatment. Tumor volumes were calculated as: V = 0.5 x L (length) x W² (width). The mice were sacrificed 35 days after injection. The tumor tissues were dissected and weighed. An aliquot of tumor tissues was collected for analysis of the expression of IRS1 and miR-128 using previously described methods (16).

Statistical analysis. Data are expressed as means ± standard deviation (SD) from three independent experiments. Statistical analyses were performed with software GraphPad Prism 5.0 software (GraphPad Software, San Diego, CA, USA). The differences between groups were analyzed using the Student’s t-test. The reverse relationship between IRS1 and miR-128 expression was assessed by Spearman’s correlation in CRC samples. P<0.05 was considered to indicate a statistically significant result.

Results

Expression of miR-128 is downregulated in CRC tissue and cell lines. In order to confirm the involvement of miR-128 in CRC, we examined the relative expression level of miR-128 in 45 CRC tissues and corresponding adjacent non-tumor tissues using RT-qPCR. The results indicated that miR-128 was greatly decreased in CRC tissues when compared with adjacent non-tumor tissues (42/45, 93.3%, P<0.01) (Fig. 1A). To investigate the clinical significance of miR-128 in CRC, 45 patients were divided into two groups according to the median value (3.36) of the miR-128 expression level in CRC tissues: high-miR-128 group (n=18) and low-miR-128 group (n=27). By statistical assay we showed that the level of miR-128 expression in tissues was significantly correlated with lymph node metastasis and TNM stage, which are all indicators of poor prognosis (all P<0.05), but not with other clinicopathological characteristics, such as age, gender and tumor size (Table I).

In addition, a panel of human CRC cell lines was first analyzed to quantify the expression level of miR-128. The results showed that the expression level of miR-128 was down-regulated in CRC cell lines when compared with that of the normal colonic cell line (NCM460) (Fig. 1B). Additionally, the expression level of miR-128 in the SW480 cell line was lowest, thus, we selected this cell line for subsequent experiments. These observations suggested that miR-128 plays a key role in CRC development.
miR-128 inhibits the proliferation and colony formation of CRC cells in vitro. The decreased expression of miR-128 in CRC tissues suggested miR-128 was a tumor suppressor. To examine the role of miR-128 in CRC growth, miR-128 mimic or miR-NC was transfected into SW480 cells. The RT-qPCR assay results showed that transfection of miR-128 mimics significantly increased miR-128 expression in SW480 cells (Fig. 2A). Then, we investigated the effects of miR-128 restoration on cell proliferation by CCK-8 assay. As shown in Fig. 2B, the proliferation of CRC cells was suppressed following transfection with miR-128 compared to cells transfection with miR-NC. Colony forming was then performed to assess the role of miR-128 in cancer cell growth. Compared with the miR-NC group, the number of SW480 colonies was significantly reduced by restoration of miR-128 (P<0.05, Fig. 2C). Taken together, the results indicated that miR-128 inhibited the proliferation and colony formation of CRC cells in vitro.

miR-128 induces apoptosis of CRC cells in vitro. The ability of miR-128 to induce apoptosis in CRC cell lines was evaluated by co-staining with Annexin V and PI. The staining demonstrated that miR-128 significantly induced apoptosis in SW480 cells compared with the miR-NC groups (Fig. 3A).
To determine the potential mechanism of cell apoptosis in vitro, the activity of caspase-3 and -8 was detected in SW480 cells following transfection with miR-128 mimic or miR-NC. It was found that caspase-3 and -8 activity was significantly increased in the miR-128 treatment groups compared to the miR-NC groups (P<0.05, Fig. 3B and C).

**miR-128 inhibits migration and colony invasion of CRC cells in vitro.** The above results showed that the level of miR-128 expression in tissues was significantly correlated with lymph node metastasis. Therefore, we hypothesized that the overexpression of miR-128 had an inhibitory effect on CRC cell migration and invasion. To confirm this hypothesis, migration and invasion assays were performed in SW480 cells transfected with miR-128 mimic by wound-healing and Transwell assays, respectively. The results showed that the overexpression of miR-128 significantly decreased the migration and invasion abilities of SW480 cells (P<0.05; Fig. 4A and B).

**IRS1 is a direct target of miR-128.** Potential targets of miR-128 were predicted using bioinformatic databases (TargetScan and PicTar). IRS1 with a critically conserved binding site was selected for further expression and function confirmation (Fig. 5A). To verify whether IRS1 is a direct target of miR-128 in CRC, a human IRS 3’UTR fragment containing the binding sites of miR-128 or the mutant sites (Fig. 5A) was cloned into the pGL3 vector. The vector along with miR-128 mimic or miR-NC were co-transfected into SW480 cells, cultured for 48 h, and luciferase activities in those cells were measured. It was found that exogenous miR-128 expression obviously suppressed the luciferase activity of wild-type IRS1 site. However, the activity of the mutant IRS1 site was not affected (Fig. 5B), which suggested that IRS1 is directly targeted by miR-128. The RT-qPCR and western blot analysis was performed to measure insulin receptor substrate 1 (IRS-1) on the mRNA and protein level in SW480 cells transfected with miR-128 mimic. We found that the expression of IRS1 was downregulated in the mRNA (Fig. 5C) and protein levels (Fig. 5D) under miR-128 mimic treatment, which indicates that miR-128 directly binds to IRS1 and inhibits the expression of IRS1. Given that IRS1 was the target of miR-128, we examined the expression of IRS1 in the 45 CRC samples and adjacent non-tumor tissues. The results of RT-qPCR showed that the expression level of IRS-1 mRNA was markedly increased in CRC tissue comparing to the adjacent non-tumor tissues (41/45, 91.1%, P<0.001) (Fig. 5E) and was inversely associated with the expression of miR-128 (Fig. 5F).

**miR-128 reduces downstream AKT signaling.** It is known that Akt signaling is a major molecular pathway under IRS1, and that Akt phosphorylates and affects multiple downstream effectors, such as cyclin D1, Bcl-2 and MMP2, which involved in cell cycle progression, apoptosis and invasion. In the present study, we found phosphorylated Akt expression was markedly reduced after transient miR-128 mimic in the SW480 CRC cell line (Fig. 6), suggesting that miR-128 suppressed Akt signaling via IRS1 reduction. We also detected cyclin D1, Bcl-2 and MMP2 protein expression in SW480 cells trans-
Figure 4. Overexpression of miR-128 inhibits CRC cell migration and invasion. (A) Cell migration was analyzed by wound healing in SW480 cells following transfection with miR-128 mimic or miR-NC. (B) Cell invasion was analyzed by Transwell chamber in SW480 cells following transfection with miR-128 mimic or miR-NC. *P<0.05, **P<0.01 vs. miR-NC. CRC, colorectal carcinoma.

Figure 5. miR-128 targets the 3’UTR of IRS-1 and downregulates its expression. (A) Predicted binding sites for miR-128 in the 3’UTR of IRS-1 and the mutations in the binding sites are shown. (B) Luciferase assay in SW480 cells co-transfected with miR-128 or miR-NC and a luciferase reporter plasmid (Wt/Mut 3’UTR IRS1). (C) Measurement of IRS1 mRNA expression levels in SW480 cells by RT-qPCR following transfection with the miR-128 mimics or miR-NC. The β-actin was used as an internal control. (D) Measurement of IRS1 expression levels in SW480 cells by western blot analysis following transfection with the miR-128 mimics or miR-NC. β-actin was used as an internal control. (E) The reverse relationship between IRS1 and miR-128 expression was assessed using the Spearman’s correlation in the CRC sample. *P<0.05, **P<0.01 vs. miR-NC. 3’UTR, 3’ untranslated region; IRS-1, insulin receptor substrate 1; CRC, colorectal carcinoma.
fected with miR-128 mimic by western blotting. We found that the expression of cyclin D1, Bcl-2 and MMP2 decreased as a consequence of downregulated Akt phosphorylation (Fig. 6). Taken together, these data suggested that miR-128-induced IRS1 underexpression potentially reduced downstream AKT signaling.

miR-128 suppresses tumor growth in nude mice by inhibiting IRS1. To examine the possibility of miR-128 as a therapeutic agent to control CRC, an SW480 xenograft tumor model was established in BALB/C nude mice. The stably transfected human CRC SW480 cells (SW480/miR-128 or SW480/miR-NC) were implanted subcutaneously into nude mice to allow tumor formation. At five weeks post-injection, the xenograft tumor volumes and weight were significantly smaller in the miR-128 group compared with those in the miR-NC group (Fig. 7A-C), indicating that miR-128 overexpression suppressed CRC tumor growth in vivo. We also detected miR-128 and IRS1 expression in xenograft tumors. We found that miR-128 expression level was upregulated in xenograft tumors (Fig. 7D), while the mRNA and protein level of IRS1 was downregulated in xenograft tumors (Fig. 7E and F). These results suggested that miR-128 suppressed tumor growth in nude mice by inhibiting IRS1.

Discussion

Emerging evidence has suggested that miRNAs play critical roles in the initiation, promotion and progression of human cancers by regulating target gene expression (7,8). Therefore, miRNAs are promising diagnostic and prognostic markers and therapeutic targets for various types of cancer, including colorectal cancer (CRC) (10,12). For example, Wang et al showed that the overexpression of miR-378-5p in CRC cells significantly decreased the proliferation and induced apoptosis by regulating the RAS/RAF/MEK/ERK pathway by targeting BRAF, suggesting that miR-378-5p is a potentially promising therapeutic agent in CRC (18). Qin et al reported that miR-145 and paxillin are significant biomarkers for proliferation and metastasis and served as targets for the development of antiproliferative and antimetastatic strategy in the therapeutic interventions of CRC (19). Fang et al suggested that miR-301a promotes CRC progression by directly downregulating SOCS6 expression, and miR-301a is a novel biomarker for the prevention and treatment of CRC (20). Zhao et al reported that miR-194 acted as a tumor suppressor in CRC by targeting the PDK1/AKT2/xIAP pathway, and may be a significant diagnostic and prognostic biomarker for
Furthermore, our immigration and invasion, and induced apoptosis in vitro significantly inhibited CRC cell proliferation, colony formation, and suppressed tumor growth in vivo. These data suggested that miR-128 acts as a novel biomarker or therapeutic agent for the prevention and treatment of CRC.

miR-128, a type of brain-enriched miRNA, has been shown to play important roles in the development of the nervous system and the maintenance of its normal physiological functions (22). Accumulating evidence has demonstrated that the aberrant expression of miR-128 was involved in the proliferation, differentiation, apoptosis, invasion and metastasis of various tumor cells (13-16). For instance, miR-128 has been shown to inhibit tumor progression, angiogenesis and lymph angiogenesis in non-small-cell lung cancer by blocking ERK, AKT and p38 signaling pathways (16). Recent findings have shown that the upregulation of miR-128 inhibited HNSCC growth by directly mediating its targets Paip2, BAG-2, H3F3B, BMI-1 and BAX in proliferation and apoptotic pathways (15). Additionally, miR-128 expression is downregulated in glioma tissue and cell lines, and restoration of miR-128 repressed growth and mediated differentiation of glioma-initiating neural stem cells by targeting oncopgenic receptor tyrosine kinases epithelial growth factor receptor and platelet-derived growth factor receptor-α and repressed gliomagenesis (14,23,24). Although it was recently shown that miR-128 induced G2-phase cell cycle arrest and inhibited cancer cell proliferation in CRC cells by targeting NEK2 (17), its roles in human CRC remain largely unclear, particularly for migration and invasion. To investigate the functions of miR-128 in CRC, we performed a rescue experiment by establishing miR-128 overexpression in SW480 CRC cells. Our results clearly demonstrated that miR-128 significantly inhibited CRC cell proliferation, colony formation, immigration and invasion, and induced apoptosis in vitro. Furthermore, our in vivo study indicated that overexpression of miR-128 suppressed NSCLC xenograft tumor growth in vivo. These results suggested that miR-128 functions as a tumor suppressor in CRC.

In view of the vital importance of miR-128, we further explored the molecular mechanisms underlying CRC biological behavior by screening and identifying its targeting gene. In the present study, insulin receptor substrate 1 (IRS-1) were identified as a target of miR-128. IRS-1, a docking protein, is highly expressed in numerous types of cancer, including CRC (25). Mounting evidence indicates that IRS1 acted as an oncogene, and was involved in various biological behaviors of tumors, such as invasion and metastasis, stemness of cancer stem cells, tumor angiogenesis and chemosensitivity, which largely contributes to tumor initiation and progression (26-28). In addition, several miRNAs have been shown to be involved in IRS1 regulation (29-32), and therefore adjusted its function with regard to occurrence and development of cancer. Consistent with these studies, to the best of our knowledge, our results first showed that IRS1 is negatively regulated by miR-128 at the post-transcriptional level by binding to the 3'UTR of IRS1 mRNA in CRC cells, and that overexpression of miR-128 was able to efficiently reduce the expression of IRS1 in CRC cells. These results suggest that IRS1 is directly targeted by miR-128.

IRS1 transmits signals from insulin or IGF receptor and activates the PI3K/Akt and MAPK pathways, both of which were critical in tumor initiation and progression (33). In the present study, we focused on the effect of downregulated IRS1 on Akt signaling, since the constitutive activation of Akt signaling play important roles in cell proliferation, cell cycle progression, apoptosis and invasion in CRC (34,35). The data from the present study show that the overexpression of miR-128 in CRC cells inhibited pAkt expression, reduced the expression of several Akt-regulated proteins including cyclin D1, Bcl-2 and MMP2. These results suggested that miR-128 inhibited CRC growth and metastasis by targeting the IRS1-regulating AKT signaling pathway.

In conclusion, the present study provides evidence that miR-128 expression is downregulated in CRC tissues and cell lines, and that its expression was significantly correlated with lymph node metastasis and TNM stage. In addition, the overexpression of miR-128 in CRC cells inhibited proliferation, migration and invasion, induced cell apoptosis in vitro, and suppressed tumor growth in vivo by targeting IRS1 and its downstream AKT signaling. These results suggest that miR-128 is a novel candidate for CRC therapeutics.

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References


