

miR-107 Promotes Proliferation and Inhibits Apoptosis of Colon Cancer Cells by Targeting Prostate Apoptosis Response-4 (Par4)

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Colorectal cancer (CRC) is one of the most common malignancies in the world, with a high incidence and a high mortality. However, the pathogenesis of CRC carcinogenesis is still unexplored. In this study, we investigated the role of miR-107 in the regulation of CRC cell proliferation and apoptosis. First, the expression of miR-107 was observed to be aberrantly increased in human CRC tumor tissues and cell lines when compared to the colonic control tissues and colon epithelial cells. Further study showed that the proliferative and apoptotic capacities of human CRC SW480 and LoVo cells were aberrantly regulated by miR-107. The proliferation of SW480 and LoVo cells was remarkably enhanced by the miR-107 mimic but suppressed by the miR-107 inhibitor when compared to the negative control. On the contrary, the apoptotic rate of both SW480 and LoVo cells was significantly inhibited by miR-107 overexpression but increased by miR-107 inhibition. In addition, we identified prostate apoptosis response-4 (Par4) as a direct target of miR-107 with a potential binding site on the 3'-UTR of mRNA, as evaluated by bioinformatics prediction and luciferase reporter assay. Par4 expression levels were significantly inhibited by the miR-107 mimic but upregulated by the miR-107 inhibitor in both SW480 and LoVo cells. Compared to the control, the increase in Par4 expression significantly inhibited the induction role of miR-107 in the proliferation of SW480 and LoVo cells, and the apoptotic rate of cells repressed by the miR-107 mimic was also reversed by Par4 overexpression. In summary, our results demonstrated that miR-107 exerts a positive role in the survival of CRC cells by directly targeting Par4. This might reveal a novel understanding about human CRC pathogenesis.

Key words: miR-107; Prostate apoptosis response-4 (Par4); Colorectal cancer (CRC); Proliferation; Apoptosis

INTRODUCTION

As endogenous regulators, microRNAs (miRNAs) are a family of small, single-stranded, noncoding RNA molecules that are 19–22 nucleotides in length and play key roles in the expression of genes¹. By binding to the specific 3'-UTR site of mRNA, most miRNAs can interact with different targets to perform tasks in a complex regulatory network for the regulation of gene expression that is involved in various biological processes, such as cell proliferation, differentiation, apoptosis, and others^{2,3}. The major way miRNA functions is at the posttranscriptional level through binding and inhibiting the translation or degradation of target mRNA to contribute to the regulatory roles.

Colorectal cancer (CRC) is one of the most common malignancies in the world, with high incidence and

mortality. CRC is the result of multistep processes in which the sequential mutations of oncogenes or tumor suppressor genes and chromosomal instability are considered to be the main oncogenic factors⁴. According to the difference in clinicopathologic entities, CRC can be classified as various histological subtypes, including sporadic, familial, and hereditary forms. In CRC cases, different types of CRC forms are exhibited in different proportions. In general, the sporadic form is the most common form of CRC; 10%–30% of CRC cases correspond to the familial form, whereas the hereditary form represents the smallest proportion⁵. In the treatment of CRC, early detection and surgical resection are the primary approaches. Although there have been significant improvements in the diagnostic method and surgical therapy, the cure rate of patients with CRC is very poor^{4,6}. Therefore, further knowledge

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about the pathology of CRC progression is urgently needed in order to improve the therapeutic strategies for human CRC.

It has been recognized that dysregulation of miRNA expression is found to be involved in the progression of various human diseases, including glioma, metastatic prostate carcinoma, and other cancers^{7,8}. In terms of CRC, aberrant regulation of miRNA has been widely reported in patients and is associated with the pathogenesis of human CRC, miR-29a, miR-135b, miR-18b, miR-124, miR-222, and miR-31⁹⁻¹¹. miR-107 has been found to be commonly dysregulated in various cancers and plays a role in the development and maintenance of tumors¹²⁻¹⁴. In this study, we found that miR-107 expression was upregulated in human CRC cells.

Prostate apoptosis response-4 (Par4), also known as PAWR, is a WT-1-interacting protein in a variety of tissues and is recognized as a tumor suppressor¹⁵. Par4 has a critical role in cell apoptosis. Accumulating evidence suggests that low expression of Par4 is associated with tumorigenesis in human cancer¹⁶⁻¹⁸. However, the question of whether dysfunction of Par4 is involved in the progression of CRC is still unexplored. In the present study, we proposed that miR-107 contributes to the pathogenesis of human CRC by targeting Par4. miR-107 expression was found to be abnormally expressed in human CRC cells and exerts a regulatory role in the survival of CRC cells by directly targeting Par4. These results might reveal a novel understanding about the pathogenesis of human CRC.

MATERIALS AND METHODS

CRC Tissues and Cells

Primary CRC biopsies and adjacent tissues were obtained from 40 patients undergoing surgical resection at The Third Xiangya Hospital of Central South University (Changsha, P.R. China). The study was approved by the ethics committee of The Third Xiangya Hospital of Central South University. All patients gave informed consent.

The human CRC cell lines SW480, HCT-116, and LoVo were purchased from ATCC (Manassas, VA, USA), and the normal colon epithelial cell line (NCM460) was purchased from Rongbai (Shanghai, P.R. China). HCT-116 cells were maintained in McCoy's 5a medium, SW480 cells were cultured in DMEM, and LoVo cells were maintained in F-12K medium containing 10% FBS at 37°C in a 5% CO₂ atmosphere. NCM460 cells were maintained in DMEM-H medium as the control.

Cell Transfection

For cell transfection, 100 nM miR-107 mimic, inhibitor, or negative control miRNA (RiboBio, Guangzhou, P.R. China) was transfected into cultured cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA)

in accordance with the manufacturer's instructions. The plasmid of Par4 (provided by Dr. Sun) was also transfected into cultured cells using Lipofectamine 2000 in the presence or absence of the miR-107 mimic. After 48 h, the transfection efficacy was evaluated by RT-PCR and Western blot assay.

Quantitative RT-PCR

Total RNA was isolated from tissues or cells using TRIzol reagent (Sigma-Aldrich, St. Louis, MO, USA). According to the manufacturer's instructions, miR-107 expression was detected by MicroRNA First-Strand Synthesis and miRNA Quantitation kits (Takara, Dalian, P.R. China), and Par4 expression was measured using the CellAmp Direct RNA Prep kit for qPCR (Takara). The reaction was 95°C for 10 min; 40 cycles of 95°C for 1 min, 63°C for 2 min, 72°C for 1 min; final 72°C for 10 min. Ct values of U6 and GAPDH expression in tissues or cells were used as the internal control. All PCRs were performed in triplicate.

Western Blot Analysis

All proteins were collected from cell lysates and counted by bicinchoninic acid (BCA) assay. Equal amounts of proteins were then separated by SDS-PAGE and transferred to a PVDF membrane. Primary antibodies were incubated with the blots [mouse anti-Par4 (1:2,000 dilution) and mouse anti-β-actin (1:2,000 dilution); both from Abcam, Cambridge, MA, USA] overnight at 4°C. The blots were then probed by specific secondary antibodies at room temperature for 1 h, and visualization with ECL was performed.

Cell Proliferation Assay

Cell proliferation was tested using cell counting kit-8 (CCK-8; Bioroot, Shanghai, P.R. China) in accordance with the manufacturer's instructions. Briefly, transfected cells were cultured for 48 h and seeded into 96-well plates (6 × 10⁴ cells/ml). The CCK-8 solution (10 μl) was then added into the cells at 12, 24, 48, and 72 h. After incubating for 4 h, the absorbance at 450 nm was measured by an ELISA plate reader (BioTek, Winooski, VT, USA).

Cell Apoptosis Assay

Cell apoptosis was evaluated by annexin V-fluorescein isothiocyanate (FITC) assay. After 48 h of transfection, transfected cells (5 × 10⁶ cells in a volume of 250 μl) were seeded into the DMEM (serum free) for another 12 h, followed by harvesting using ice-cold phosphate-buffered saline and resuspending using binding buffer. Cells were then treated with 0.5 μg/ml propidium iodide (PI) and 0.6 μg/ml annexin V-FITC for 15 min in the dark, and the apoptosis rate of cells was analyzed by the FACSCalibur™ system (Becton Dickinson, San Jose, CA, USA).

Luciferase Reporter Assay

The luciferase assay was conducted as described previously¹⁹. In brief, the 3'-UTR of Par4 mRNA was cloned into pGL3 vector (Promega, Madison, WI, USA). QuikChange Lightning Site-Directed Mutagenesis Kit (Stratagene, San Diego, CA, USA) was applied to introduce site-directed mutagenesis into the predicted miR-107 binding site on the mRNA of Par4. The recombinant vectors were then transfected into cultured CRC cells in the presence or absence of the miR-107 mimic for 36 h. The luciferase activity was then tested by Dual Luciferase Assay (Promega).

Statistical Analysis

All data are expressed as mean±SEM. SPSS15.0 was used to analyze the differences between groups by one-way ANOVA. All experiments were performed in triplicate. A value of $p < 0.05$ was considered statistically significant.

RESULTS

miR-107 Is Upregulated in Human CRC Tissues and Cells

To determine the potential role of miR-107 in human CRC, we first identified the expression of miR-107 in the tumor tissues of CRC patients. miR-107 was significantly increased in tumor tissues while it was maintained at relatively low expression levels in adjacent colonic tissues (Fig. 1A). We further investigated the level of miR-107

expression in human CRC cell lines SW480, HCT-116, and LoVo cells. miR-107 expression levels were aberrantly upregulated in the SW480, HCT-116, and LoVo cells when compared with normal colon epithelial cells NCM460 (Fig. 1B).

miR-107 Promotes the Survival of Human CRC Cells

To further identify the possible effect of high miR-107 levels on human CRC cells, we employed the specific mimic and inhibitor of miR-107 to evaluate the effects of miR-107 on cell proliferation and apoptosis in human CRC. Because of the difference in the expression of miR-107, SW480, and LoVo cells, these were used as cell models in subsequent experiments. The efficiency of the mimic and inhibitor was confirmed using the RT-PCR assay. Compared to the negative control miRNA, the specific mimic significantly increased the expression of miR-107 in both SW480 and LoVo cells, whereas it was decreased by the inhibitor (Fig. 2A).

In the CCK-8 assay, the effect of miR-107 on the proliferation of CRC cells was examined. The proliferation of the SW480 and LoVo cells was remarkably enhanced by the miR-107 mimic compared to the negative control, whereas the miR-107 inhibitor significantly suppressed the proliferation capacity of these two CRC cells (Fig. 2B). Furthermore, we investigated the apoptosis rate of SW480 and LoVo cells. Compared to the control, the apoptosis rate of both SW480 and LoVo cells was significantly inhibited by miR-107 overexpression but increased by miR-107 inhibition (Fig. 2C).

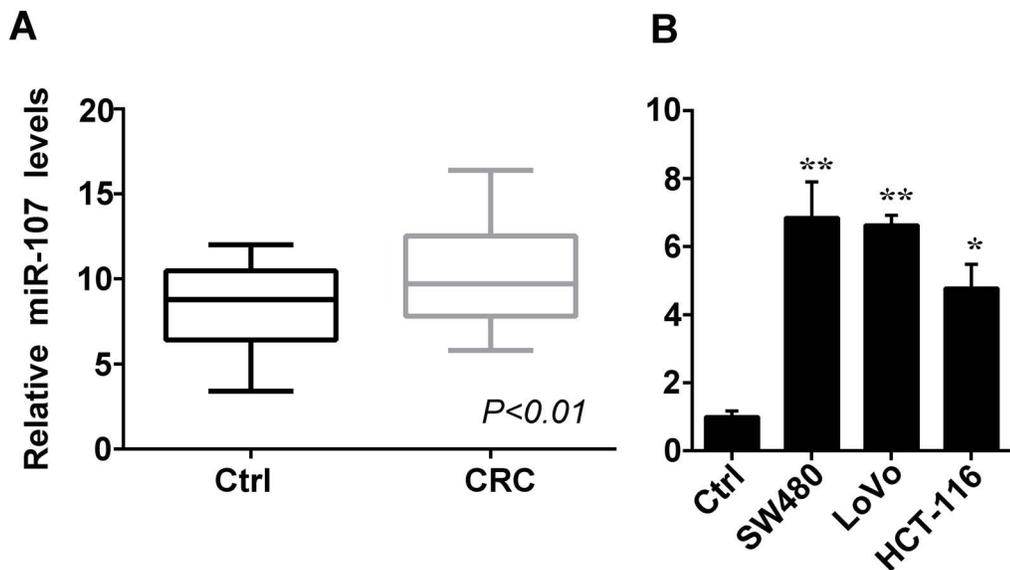


Figure 1. miR-107 expression is increased in CRC tumor tissues and cells. (A) The miR-107 expression was examined in human CRC tumor tissues as well as in adjacent colonic tissues (Ctrl) by RT-PCR ($*p < 0.05$ vs. Ctrl). (B) miR-107 expression was measured in human CRC cell lines (SW480, HCT-116, and LoVo) as well as in the normal colon epithelial cell line NCM460 (Ctrl) ($**p < 0.01$, $*p < 0.05$ vs. Ctrl).

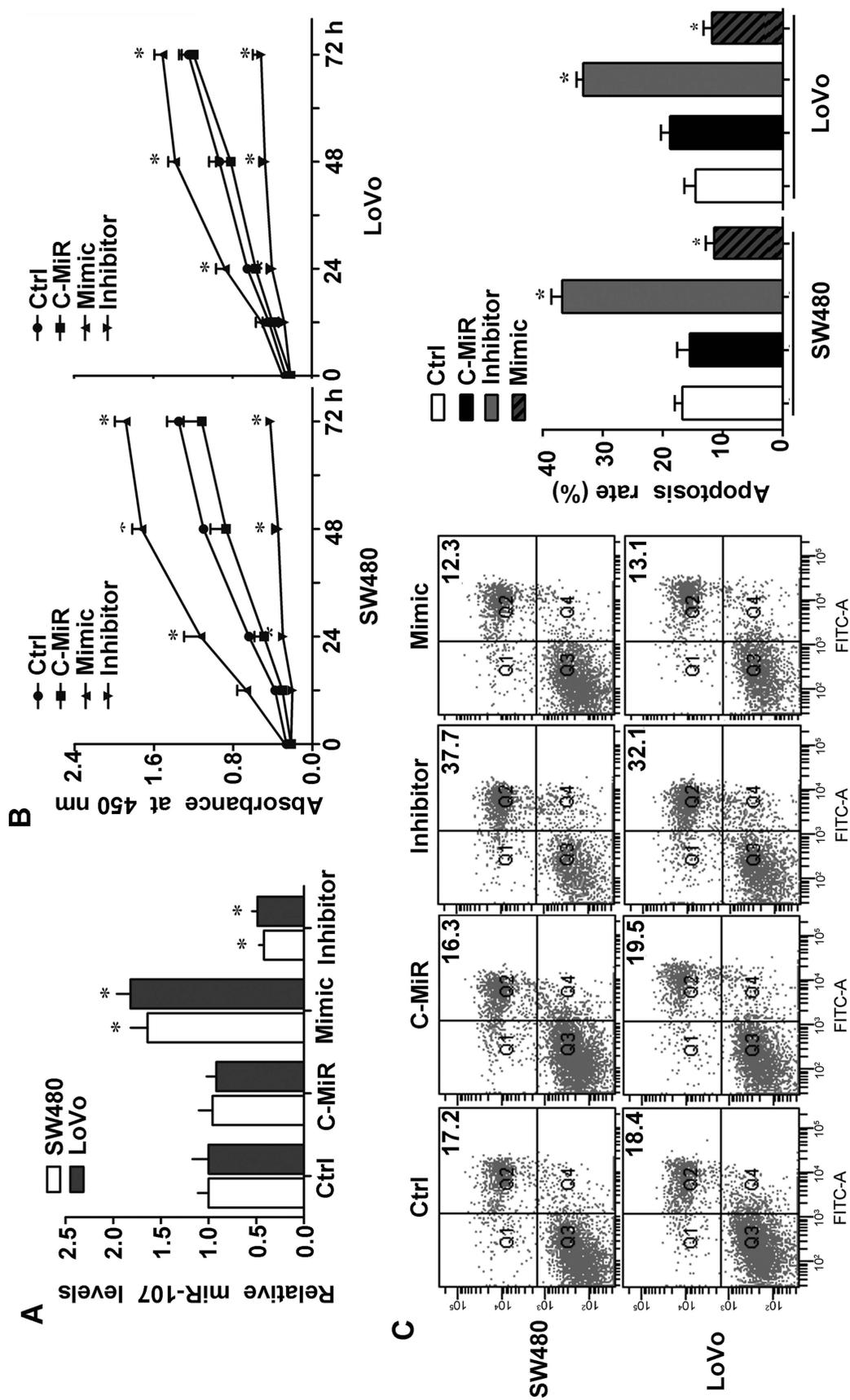


Figure 2. miR-107 promotes the survival of human CRC cells. SW480 and LoVo cells were transfected by the miR-107 inhibitor, mimic, or negative miRNA (C-MiR). (A) After 48 h of transfection, miR-107 expression was tested by RT-PCR assay in cells. (B) CCK-8 assay was performed to detect the proliferation of CRC cells at 12, 24, 48, and 72 h, respectively. (C) Flow cytometric analysis was performed to evaluate the apoptosis rate of transfected cells (* $p < 0.05$ vs. Ctrl).

Par4 Is the Target of miR-107

Par4 is a tumor suppressor in various cancers, including human CRC¹⁵. We predicted the potential targets of miR-107 using Microna.org and TargetScan databases and found that there is a possible binding site of miR-107 in the 3'-UTR of Par4 mRNA (Fig. 3A). To identify the prediction and elucidate the underlying mechanism by which miR-107 regulates CRC cell survival, we conducted the luciferase reporter assay in SW480 and LoVo cells. The wild or mutant 3'-UTR of Par4 mRNA was cloned into the luciferase vector (Fig. 3A). The luciferase activity of wild Par4-3'UTR was strongly reduced by the miR-107 mimic, but there was no difference in the luciferase activity of mutant Par4-3'UTR in CRC cells (Fig. 3B).

Furthermore, we determined that the Par4 expression level was significantly inhibited by the miR-107 mimic but upregulated by the miR-107 inhibitor in both SW480 and LoVo cells (Fig. 3C).

Par4 Is Involved in the miR-107-Mediated Regulation of CRC Cell Survival

Previous studies reported that Par4 is a proapoptotic factor and is required for cell apoptosis²⁰. To identify whether Par4 is involved in the miR-107-mediated regulation of CRC cell survival, we further employed a Par4 plasmid to specifically induce the expression of Par4 in

both SW480 and LoVo cells. The efficiency of the Par4 plasmid was confirmed by RT-PCR assay (Fig. 4A). Compared with the negative control, Par4 expression was strongly enhanced by the specific recombinant plasmid in both CRC cells.

The increase in Par4 expression significantly inhibited the induction role of miR-107 in the proliferation of SW480 and LoVo cells (Fig. 4B). On the contrary, the apoptosis rate of SW480 and LoVo cells repressed by the miR-107 mimic was also reversed by Par4 overexpression compared to the control (Fig. 4C).

DISCUSSION

In this study, we found that miR-107 expression was aberrantly upregulated in human CRC cells. Endogenous miRNAs play a crucial role as key regulators of gene expression in the physiological or pathological processes of human development and diseases²¹. Differential expression of miRNAs has been reported in previous studies about CRC, and the dysregulation of miRNAs has been considered to play a positive or negative role in colorectal carcinogenesis, including miR-29a, miR-135b, miR-18b, miR-124, miR-222, and miR-31²²⁻²⁴.

miR-107 plays different roles in the physiological processes and progression of many human diseases²⁵⁻²⁸. Dysfunction of miR-107 also exerts a tumor oncogenic

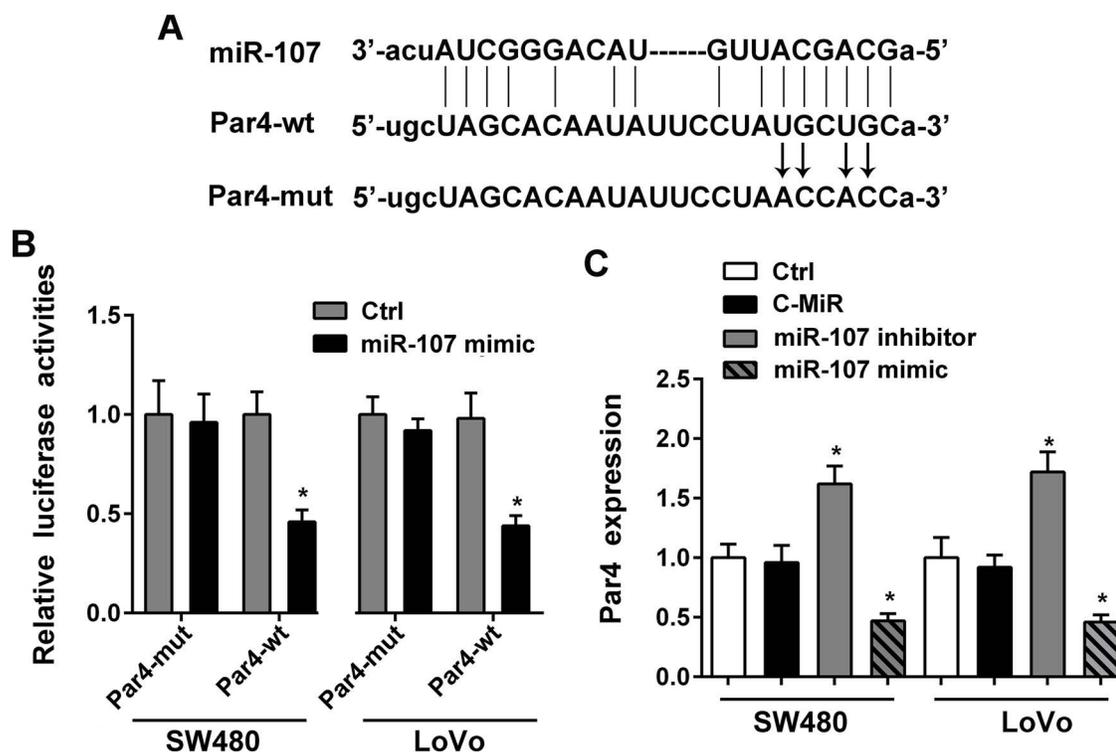


Figure 3. Par4 is the target of miR-107. (A) The potential binding sites of miR-107 in the 3'-UTR of Par4 mRNA. (B) Luciferase activities were measured in SW480 and LoVo cells after transfection by wild Par4-3'UTR (Par4-wt) or mutant Par4-3'UTR (Par4-mut). (C) The expression of Par4 in SW480 and LoVo cells was examined by RT-PCR assay (* $p < 0.05$ vs. Ctrl).

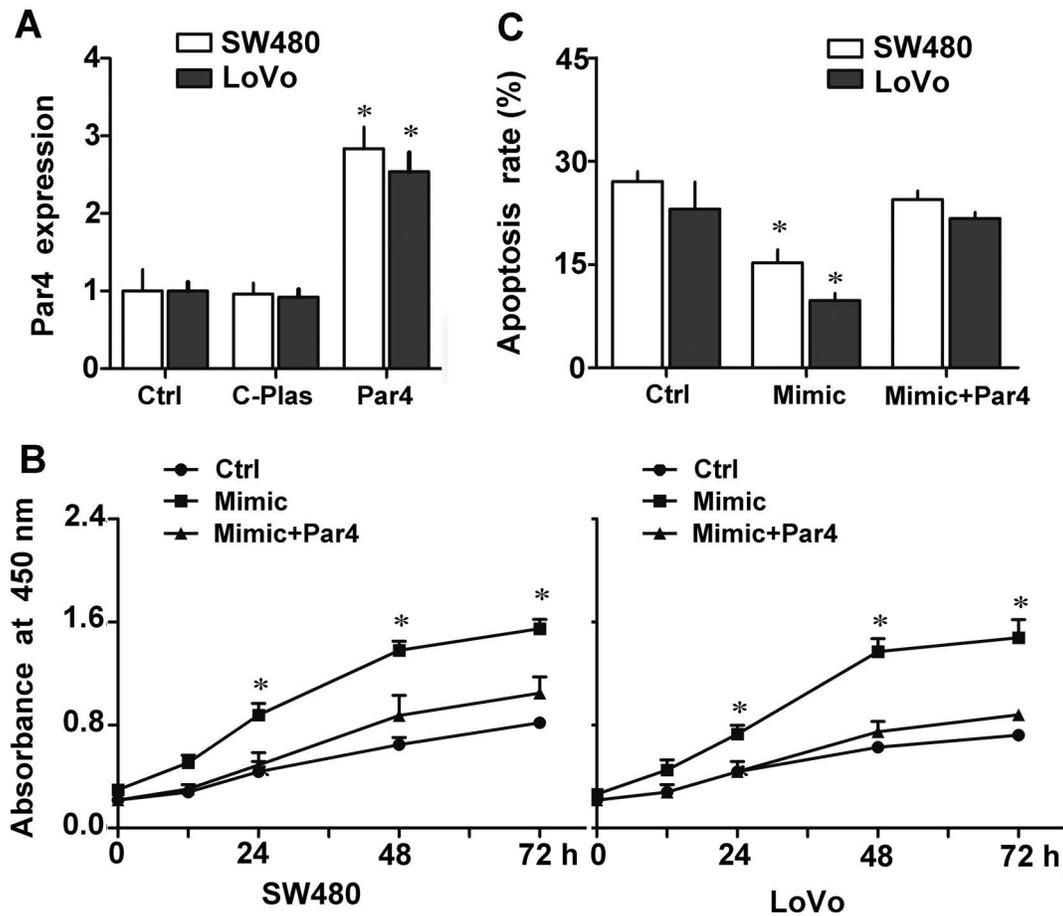


Figure 4. Par4 is involved in the miR-107-mediated regulation of CRC cell survival. SW480 and LoVo cells were transfected with Par4 plasmid or negative plasmid (C-Plas). (A) The expression levels of Par4 were tested by RT-PCR assay in both CRC cells. Cell proliferation (B) and apoptosis (C) were then measured in SW480 and LoVo cells transfected with the Par4 plasmid in the presence or absence of the miR-107 mimic (* $p < 0.05$ vs. Ctrl).

role in tumorigenesis. Chen et al. reported that the passenger miR-107 was largely expressed in mice as well as in humans and could promote tumor progression via various signal pathways²⁹. In another study, the increase in miR-107 expression was found to be associated with gastric adenocarcinoma. A common genetic variation in the promoter of miR-107 is associated with the susceptibility and survival of gastric adenocarcinoma³⁰. In human CRC, miR-107 expression was also associated with the tumorigenesis of CRC and is involved in the diagnosis and prognosis of patients with CRC^{31,32}. In the present study, we further demonstrated a novel role for miR-107 in CRC. miR-107 expression was significantly upregulated in human CRC tissues as well as in cultured CRC cell lines. The dysregulation of miR-107 was also associated with the regulation of survival of CRC cells by promoting cell proliferation and inhibiting apoptosis, contributing to human CRC tumorigenesis.

Par4 is encoded by the Pawr gene and is also known as PAWR. In various tissues, Par4 could interact with the WT-1 protein and play an important regulatory role in cell apoptosis³³. As a tumor suppressor, Par4 has been identified to be expressed at low levels in multiple human cancers and is associated with the tumorigenesis of cancers³⁴. By online bioinformatic prediction and luciferase reporter assay, we confirmed that there is a binding site of miR-107 in the 3'-UTR of Par4 mRNA, and Par4 is a direct target of miR-107 in human CRC cells. The expression level of Par4 was significantly repressed by miR-107 in human CRC cells, suggesting the involvement of miR-107 and Par4 in human CRC tumorigenesis. Our result is consistent with a previous report showing that miR-107 inhibited cardiac aging and cardiac fibroblast cellular senescence as a negative modulator by targeting Par4 and regulating the downstream proteins, including FAK, CEBPB, vimentin, N-cadherin, Oct4, and Sca-1²⁰.

Another approach we took to evaluate the function of miR-107 was to determine the possible mechanisms by which miR-107 mediated the regulation of CRC cell survival. In previous studies, Par4 has been reported to be a crucial regulator of tumor cell survival. Induced Par4 expression could enhance death in some cancer cells, and the downregulation of Par4 expression might be a prognostic factor in cancer³⁵. Herein we also found the involvement of miR-107 and Par4 in the regulation of human CRC cell survival. The increase in Par4 expression significantly inhibited the induction role of miR-107 in the proliferation of CRC cells. On the contrary, the apoptosis rate of CRC cells repressed by the miR-107 mimic was also reversed by Par4 overexpression. These findings indicate that miR-107 regulated the survival of CRC cells by targeting Par4.

In summary, our results demonstrated that an increased miR-107 level exerts a positive role in the survival of CRC cells by directly targeting Par4, contributing to colorectal carcinogenesis. This might reveal a novel understanding about the human CRC pathogenesis.

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