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Role of *hsa_Circ_0001821* in Colorectal Cancer Pathogenesis and Response to 5-Fluorouracil through miR-203a-3p/*FGF-2* Axis

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ABSTRACT

Background: Chemoresistance, the primary cause of disease relapse and treatment failure, poses a significant challenge in the treatment of CRC. Understanding the molecular mechanisms that underlie the pathogenesis and chemoresistance of colorectal tumor cells, as well as identifying novel therapeutic strategies, would be crucial. This study aimed to evaluate the role of *hsa_Circ_0001821* in response to 5-FU in CRC, a topic that has not been examined to date.
Methods: The current study investigated the effect of *hsa_Circ_0001821* suppression using interfering RNAs on the response of colorectal tumor cells to 5-FU. The expression levels of *hsa_Circ_0001821*, *hsa-miR-203a-3p*, *BAX*, *BCL-2*, and *FGF-2* were determined via quantitative RT-PCR. Cell survival, migration rate, and apoptosis induction of colorectal tumor cells subjected to 5-FU treatment were assessed using the MTT test, scratch assay, and flow cytometry analysis, respectively.
Results: Knockdown of *hsa_Circ_0001821* with siRNA increased the expression level of *hsa-miR-203a-3p* and decreased the expression level of *FGF-2*. Additionally, the knockdown of *hsa_Circ_0001821* enhanced the sensitivity of colorectal tumor cells to 5-FU. This circRNA significantly affected the viability, apoptosis, and migration of tumor cells.
Conclusion: Our study reveals the potential role of *hsa_Circ_0001821* in controlling the tumor cell viability and response to 5-FU by targeting the *hsa-miR-203a-3p*/*FGF-2* axis. These findings enhance our understanding of the molecular mechanisms that influence chemotherapy response in CRC, paving the way for the identification of more effective treatments for this disease. ***DOI: 10.61882/ibj.4942***

Keywords: Colorectal Neoplasm, Antineoplastic Agents, MicroRNAs, Circular RNA

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List of Abbreviations:
5-FU: 5-fluorouracil; **circRNAs:** circular RNA; **CRC:** colorectal cancer; **FGF:** fibroblast growth factor; **qRT-PCR:** quantitative reverse transcription PCR

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INTRODUCTION

Colorectal cancer is one of the most significant contributors to cancer-related mortality and morbidity globally, affecting men and women with nearly equal frequency[1,2]. CRC treatment strategies including surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, and combination therapies are employed based on factors such as tumor location and stage at diagnosis[3,4]. Chemoresistance, which limits the efficacy of chemotherapy, poses a significant challenge in CRC treatment and influences patient prognosis. It is also the primary cause of treatment failure and disease relapse, especially in the majority of metastatic cases[5]. Chemoresistance arises from intrinsic or acquired resistance to anticancer drugs, presenting a substantial obstacle to effective cancer treatment[6]. Studies on the human genome have shown that non-coding RNAs contribute to different biological processes, including carcinogenesis[7]. The abnormal function of non-coding RNAs regulates critical cellular mechanisms, such as autophagy, apoptosis, cell cycle, and other metabolic processes related to chemoresistance[7,8].

CircRNAs are back-spliced long non-coding RNAs that play a significant role in regulating various biological functions in cancer, including proliferation, apoptosis, migration, invasion, DNA damage, and treatment responses[9,10]. CircRNAs influence cellular functions through several mechanisms, such as acting as sponges for miRNAs and proteins. They also act as transcriptional and translational regulators, with some circRNAs capable of being translated[11]. The miRNA sponge mechanism, a widely recognized function of circRNAs, modulates the expression level of target genes by sponging specific miRNAs[12]. Results of recent studies have indicated that *hsa_Circ_0001821* (circ-PVT1) is dysregulated in diverse neoplasms, such as gastric cancer, hepatocellular carcinoma, and liver cancer, and may serve as a diagnostic biomarker[13,14]. It has been reported that circ-PVT1 affects the response to cisplatin and doxorubicin in osteosarcoma cells by targeting ABCB1[15]. Similarly, *hsa-miR-203a-3p*, which is also dysregulated in multiple neoplasms such as bladder cancer, esophageal cancer, and hepatocellular carcinoma, contributes to the regulation of biological processes such as tumor growth and metastasis[16,17]. Furthermore, it was disclosed that *hsa_Circ_0001821* impacts the development and progression of hepatocellular carcinoma by sponging *hsa-miR-203a-3p*[18]. Additionally, bioinformatics analysis using the CircInteractome database (https://circinteractome.nia.nih.gov/) has indicated that *hsa_Circ_0001821* can target hsa-miR-203a-3p, limiting its function through a 7mer-M8 binding site with a score of -0.019. A previous study has demonstrated that hsa-miR-203a-3p controls tumor cell migration and growth in pancreatic cancer by targeting FGF-2[19].

Considering the important role of *hsa_Circ_0001821* and hsa-miR-203a-3p in cancer pathogenesis, along with the existing uncertainties regarding the role of *hsa_Circ_0001821* in response to therapeutic agents, this study sought to elucidate the function of *hsa_Circ_0001821* in the progression of colorectal neoplasm and its impact on the response to 5-FU. By investigating the hsa-miR-203a-3p/FGF-2 axis, we could gain insights into the relationship between circRNAs, cancer biology, and treatment response.

MATERIALS AND METHODS

Cell culture

The HCT116 human CRC cell line was obtained from the Pasteur Institute of Iran (Tehran). The cells were cultured in DMEM (Gibco, USA) complemented with 10% FBS (Gibco) in a 5% CO_2 atmosphere with high relative humidity at 37 °C.

Quantitative reverse transcription PCR

About 4×10^5 cells were seeded per well of a six-well plate. Following an overnight cell attachment, treatments with siRNA and 5-FU were performed. Total RNA extraction and first-strand cDNA synthesis for circRNA and target genes were carried out using TRIzol solution (Life Technologies, USA) and the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher, USA), respectively. The first-strand synthesis of cDNA for *hsa-miR-203a-3p* and U6 was performed utilizing the stem-loop method. The expression levels of *hsa-miR-203a-3p*, *hsa_Circ_0001821*, *BAX*, *BCL-2*, and *FGF-2* were evaluated using specifically designed primer pairs. *GAPDH* was used as the reference gene for normalizing *hsa_Circ_0001821*, *BAX*, *BCL-2*, and *FGF-2*, while *U6* served as a housekeeping gene for normalizing *hsa-miR-203a-3p* (Table 1). To measure the expression levels of circRNAs, miRNA, and the target genes, the LightCycler® 96 Real-Time PCR System (Roche, Germany) was used. For the evaluation of *hsa-miR-203a-3p* and *U6*, a two-step protocol was followed: 95 °C for 15 minutes, followed by 40 cycles of 95 °C for 15 seconds and 64 °C for 60 seconds. In order to evaluate the expression level of *hsa_Circ_0001821*, *BAX*, *BCL-2*, *FGF-2*, and *GAPDH*, a three-step protocol was implemented: 95 °C for 15 minutes, and then 40 cycles of 95 °C for 15 seconds, 50-60 °C for 30 seconds, and 72 °C for 30 seconds.

Table 1. The sequences of the designed primers for miRNA, circRNA, and target genes

Genes	Primer sequences	Product length (bp)	Accession	Ta (°C)
GAPDH	F: AAGGCTGTGGGCAAGGTCATC R: GCGTCAAAGGTGGAGGAGTGG	248	NM_001289746.2	58
U6	F: GCTCGCTTCGGCAGCACATATAC R: CGAATTTGCGTGTCATCCTTGCG	89	NR_004394	60
hsa_Circ_0001821	F: TTCCTGGTGAAGCATCTG R: GCACAGCCATCTTGAGG	108	-	61
BAX	F: CAGAGGCGGGGGATGATTG R: TGTCCAGCCCATGATGGTTC	198	NM_004324.4	56
BCL-2	F: TGGAGAGTGCTGAAGATTGA R: GTCTACTTCCTCTGTGATGTTGTAT	121	NM_000633.3	54
FGF-2	F: AGCGACCCTCACATCAAGC R: TCATCCGTAACACATTTAGAAGCC	134	NM_002006.6	53
hsa-miR-203a-3p	F: AATCGGCGGTGAAATGTTTAG R: GTCGTATCCAGTGCAGGGT	75	MIMAT0000264	61

Cell transfection

A specific siRNA targeting the covalently closed junction of *hsa_Circ_0001821* (5'-UGGGCUUGAGGC CUGAUCU-3') was synthesized by Microsynth (Switzerland). After seeding about 4×10^5 cells per well in six well plates and cell attachment overnight, transfection was carried out using the Si-Circ-0001821 with the X-tremeGENE™ siRNA Transfection Reagent (Sigma-Aldrich, Steinheim, Germany) as per the manufacturer's instructions. Briefly, for the transfection of Si-Circ-0001821, the medium was replaced with a medium lacking FBS and penicillin-streptomycin. Then, the serum free medium containing complex of Si-Circ-0001821 and transfection reagent was dispensed dropwise to each well.

Cell viability assay

MTT assay is a method to evaluate cell survival following treatment[20]. First, approximately 8×10^3 of cells were seeded into each well of a 96-well plate, and then treatment was performed. Following 48 hours of exposure to varying concentrations of 5-FU (0–136 µM), MTT solution was added, and the plate was incubated at 37 °C for 4 hours. After dissolving the formazan crystals in 100 µl of DMSO, the optical density of the solutions in the plate was measured using an ELISA reader (Agilent BioTek Epoch Microplate Spectrophotometer, Winooski, Vermont, U.S.) at 570 nm, and cell viability was subsequently assessed[21].

Scratch assay

Approximately 1×10^5 of HCT116 cells were plated per well in 24-well plates. Upon reaching ~80% confluency, various treatments, including Si-NC, Si-Circ-0001821, 8.5 µM of 5-FU, and 8.5 µM of 5-FU + Si-Circ-0001821, were applied. After creating a scratch in the middle of each well and washing the detached cells, the wells were observed under a microscope at specific time intervals to monitor cell migration into the scratched area. We used ImageJ (version 1.49) software to quantify cell migration based on the microscopic images of the wound healing process.

Cell death assay

The apoptotic cell death rate was assessed utilizing the FITC-Annexin V Apoptosis Detection Kit (Invitrogen, Carlsbad, CA, USA). To evaluate the apoptosis rate, HCT116 cells were seeded in six-well plates at a density of 4×10^5 per well. After cell attachment overnight, treatment with Si-NC, Si-Circ-0001821, 8.5 µM of 5-FU, and 8.5 µM of 5-FU + Si-Circ-0001821 was applied. Following 48 hours of treatment, human CRC cells were detached and washed with cold PBS. Afterwards, the cells were labeled with propidium iodide and FITC-Annexin V and incubated on ice in the dark. The flow cytometry analysis was conducted using a flow cytometer (Thermo Fisher), and the percentage of apoptosis were evaluated with FlowJo software (version 10.8.1).

Statistical analysis

Statistical analysis was carried out using SPSS software (version 16). An independent sample t-test was utilized to evaluate statistical differences between the groups. For all statistical tests, p values below 0.05 were deemed statistically significant.

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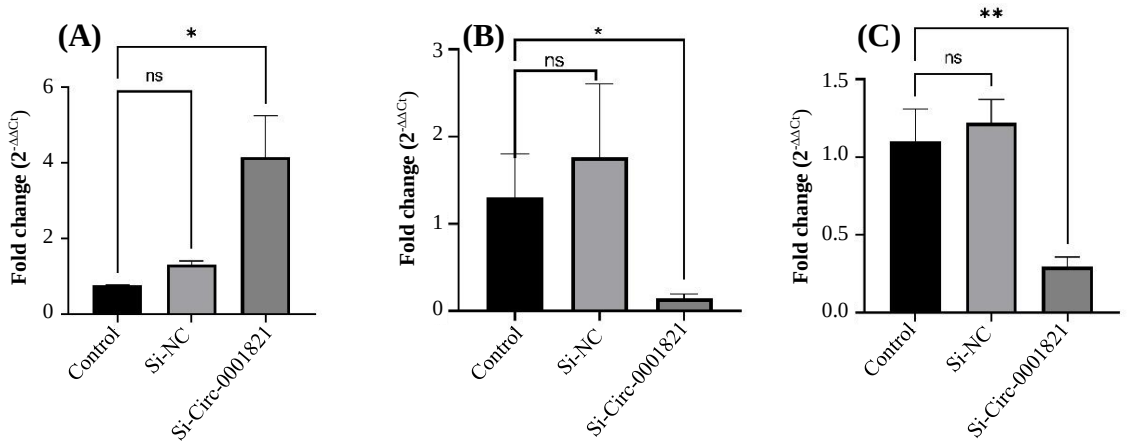

Fig 1. The expression level of (A) *hsa-miR-203a-3p*, (B) *hsa_Circ_0001821*, and (C) *FGF-2* following the *hsa_Circ_0001821* knockdown in HCT116 cell line. The data show that by suppressing *hsa_Circ_0001821*, *hsa-miR-203a-3p* is upregulated, while the expression level of *FGF-2* genes is significantly downregulated ($^{*}p < 0.05$, $^{**}p < 0.01$). ns: not significant

RESULTS

Suppression of *hsa_Circ_0001821* resulted in the downregulation of *FGF-2*

The transfection efficiency of Si-Circ-0001821 was evaluated using qRT-PCR, which showed a significant downregulation of *hsa_Circ_0001821* in the transfected cells compared to the control group (fold change = -6.74; $p < 0.05$). Furthermore, the results of real-time PCR disclosed that inhibiting *hsa_Circ_0001821* with interfering RNA resulted in the upregulation of *hsa-miR-203a-3p* (fold change = 4.15; $p < 0.05$) and the downregulation of *FGF-2* (fold change = -3.37; $p < 0.01$). These findings confirm that *hsa_Circ_0001821* functions as a molecular sponge for *hsa-miR-203a-3p*, enhancing the *FGF-2* expression level in HCT116 cells (Fig. 1).

Inhibition of *hsa_Circ_0001821* led to a reduction of HCT116 cell viability and migration

MTT assay results indicated that cell viability after 48 hours of 5-FU treatment reduced due to the knockdown of *hsa_Circ_0001821*. Furthermore, the IC_{50} value for the combination of 5-FU and Si-Circ-0001821 was lower compared to 5-FU treatment alone, indicating an enhanced effect of 5-FU in reducing cancer cell viability (Fig. 2). Scratch assay results demonstrated that the suppression of *hsa_Circ_0001821* inhibited the migration of HCT116 cells. When the inhibition of *hsa_Circ_0001821* was combined with 5-FU treatment, migration further reduced compared to both the untreated and 5-FU-treated groups (Fig. 3).

Knockdown of hsa_Circ_0001821 increased the apoptosis rate of HCT116 cells

The study employed flow cytometry to assess apoptosis levels. The findings revealed that silencing hsa_Circ_0001821 could significantly induce apoptosis and reduce cell survival in HCT116 cells. Additionally, combining 5-FU with hsa_Circ_0001821 silencing enhanced apoptosis in these cells (Fig. 4A and 4D). We also found that the combination of 5-FU and Si-Circ-0001821 resulted in an increase in the expression level of *BAX* (Fig. 4B), an inducer of apoptosis ($p < 0.001$). In contrast, the expression level of *BCL-2*, an inhibitor of programmed cell death, decreased ($p < 0.01$; Fig. 4C).

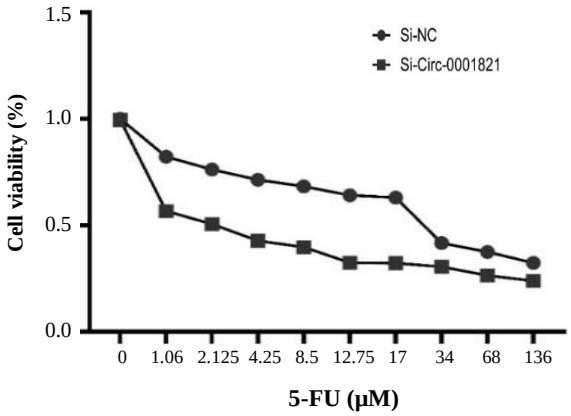

Fig 2. Effects of *hsa_Circ_0001821* knockdown on CRC cell viability. The effect of *hsa_Circ_0001821* knockdown was evaluated by MTT assay. The results indicated that the use of Si-Circ-0001821 led to a significant decrease in cell viability in HCT116 cells.

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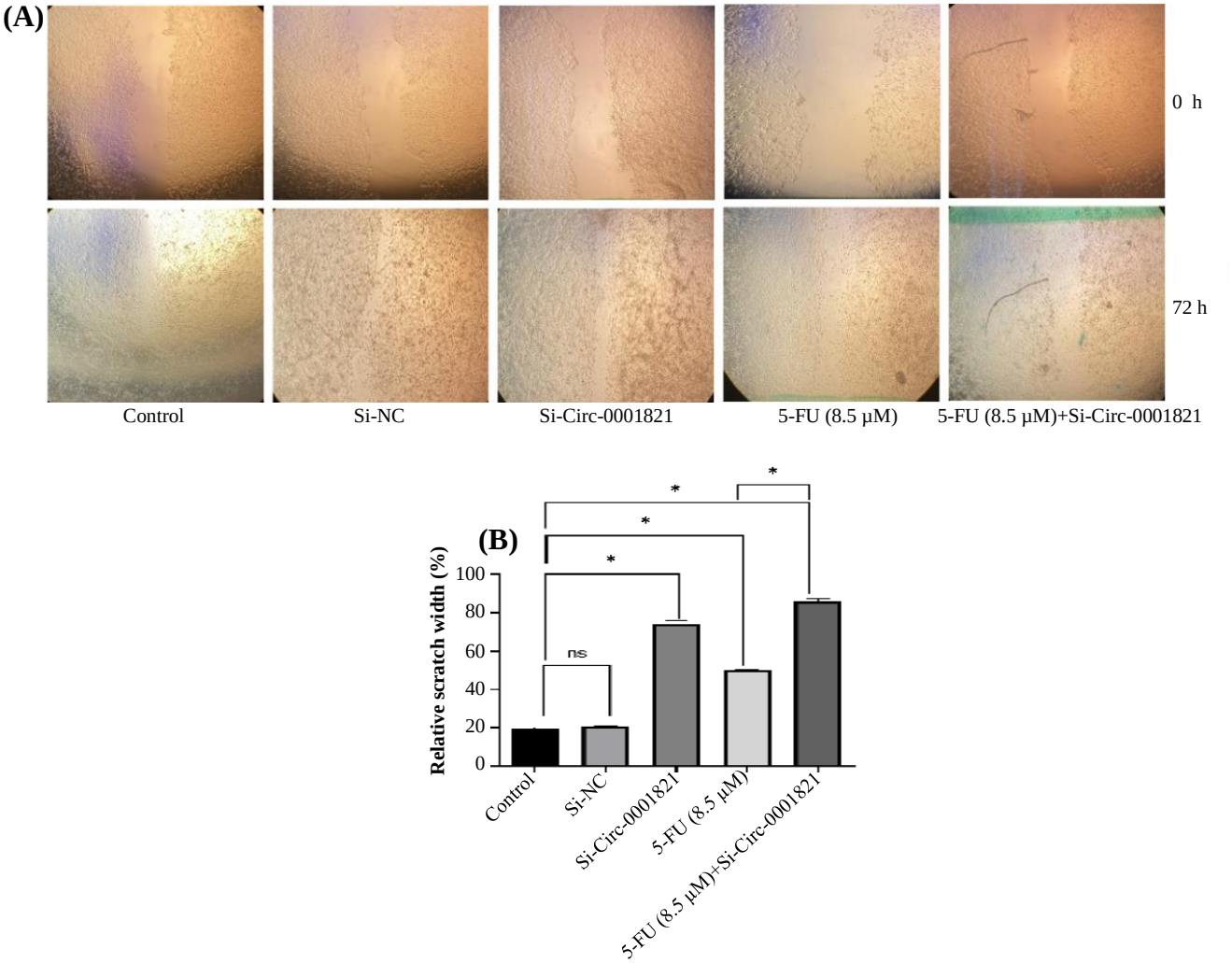

Fig. 3. Effect of *hsa_Circ_0001821* silencing on the migration of HCT116 cells. (**A)** Representative optical microscopy images of the scratch assay used to determine the rate of cell migration. (**B)** The data show that in the group treated with Si-Circ-0001821 and 5-FU, the amount of cell migration was significantly inhibited compared to the control group ($^{*}p < 0.05$). ns: not significant

DISCUSSION

Chemoresistance, including both intrinsic and acquired resistance, results in poor prognosis, metastasis, and disease recurrence, making it the primary obstacle to effective cancer therapy. Considering the significant impact of chemoresistance on the outcomes of CRC patients, it is essential to understand the molecular mechanisms underlying the response to therapeutic agents. Therefore, the current study designed to investigate the role of *hsa_Circ_0001821* in the response to 5-FU by targeting the *hsa-miR-203a-3p*/*FGF-2* axis[22,23].

The results of this study revealed that silencing *hsa_Circ_0001821* using siRNA led to an increase in the expression level of *hsa-miR-203a-3p* and a decrease in the expression of *FGF-2*. A primary focus of the present study was to examine the potential mechanism by which *hsa_Circ_0001821* contributes to increasing the resistance of HCT116 cells to 5-FU. The findings supported the involvement of *hsa-miR-203a-3p* and *FGF-2* as targets of *hsa_Circ_0001821* in the cellular response to 5-FU. Studies have indicated that circ-PVT1, which acts as an oncogene, is dysregulated in numerous malignancies, such as gastric cancer, esophageal cancer, and colorectal neoplasm. Furthermore, circ-PVT1 has a potential role in the chemoresistance of several neoplasms, such as osteosarcoma, non-small cell lung cancer, and gastric cancer[24,25]. Study by Liu et al. have exhibited that the expression of hsa_circ-PVT1 elevates in CRC and contributes to the regulation of cell viability, invasion, and stemness of malignant cells[26]. Likewise, Yao et al. have shown that circ-PVT1 regulates the response of gastric cancer cells to cisplatin by influencing apoptosis, autophagy, and invasion[27].

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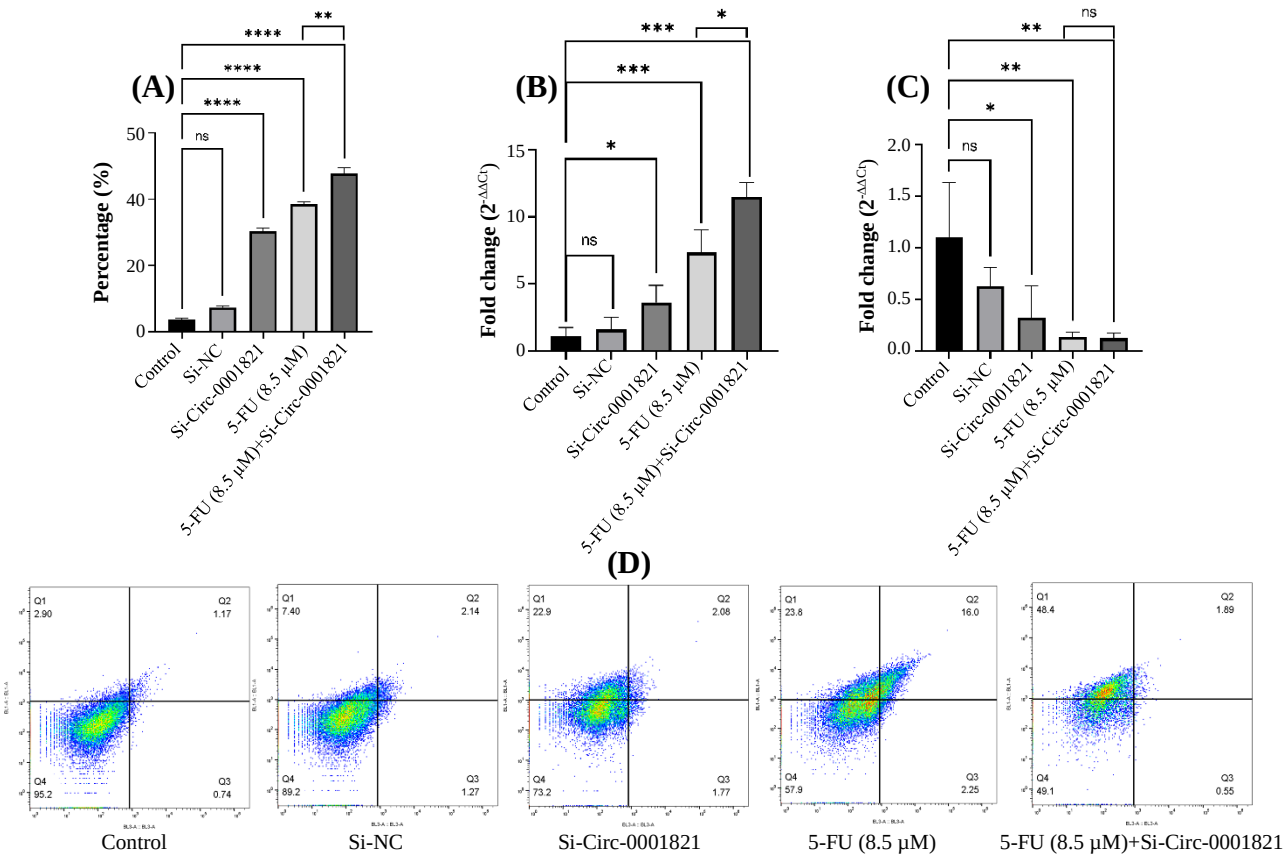

Fig 4. The *hsa_Circ_0001821* silencing induced apoptosis in CRC cells. (A) The flow cytometry results indicated that the silencing *hsa_Circ_0001821* could significantly induce apoptosis. Relative expression of (B) *BAX* and (C) *BCL-2* genes was evaluated with real-time PCR and indicated that treatment of HCT116 cells with Si-Circ-0001821 and 5-Fu resulted in increasing the expression level of *BAX* and decreasing the expression level of *BCL-2* ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$). (D) Dot blot diagrams were obtained by flow cytometry method. ns: not significant

Our results exhibited that inhibiting *hsa_Circ_0001821* suppressed the expression level of *FGF-2* and affected the growth, migration, and apoptosis of colorectal tumor cells. Moreover, the balance between the *BAX* and *BCL-2* genes was disrupted following treatment with interfering RNA (Si-Circ-0001821), resulting in a significant elevation in *BAX* and a decrease in *BCL-2* expression levels in the treatment groups.

FGF-2, a prominent member of the FGF family, is widely recognized as a key pro-angiogenic growth factor. It enhances cell viability, migration, and endothelial cell growth, serving a critical role in tumor progression and angiogenesis across various malignancies, including lung cancer, kidney cancer, and CRC[28]. In 2011, Matsuda et al. showed that the overexpression of *FGF-2* is significantly correlated with increased invasiveness in CRC[29]. A survey by Entezari et al. have revealed that the upregulation of *hsa-miR-203a-3p* elevates the BAX/BCL-2 ratio, leading to the induction of apoptosis in breast cancer cells[30]. Research has shown that FGF-2 prevents apoptosis by downregulating BAX and upregulating BCL-2. A 2019 study by Qian et al. have demonstrated that *hsa-miR-203a-3p* is dysregulated in colorectal tumor tissues and controls biological functions such as the growth and apoptosis of tumor cells[31].

Considering the findings of the current study, *hsa_Circ_0001821* fulfills a crucial role in the control of tumor cell viability and migration by influencing the *hsa-miR-203a-3p*/FGF-2 axis. Moreover, the knockdown of *hsa_Circ_0001821* sensitizes colorectal neoplasm cells to 5-FU by inducing apoptosis.

CONCLUSION

The findings of the current study suggest that *hsa_Circ_0001821* could be involved in controlling the viability, migration, and sensitivity of colorectal tumor cells to 5-FU through the *hsa-miR-203a-3p*/FGF-2 axis. These results offer valuable perception into the

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molecular mechanisms underlying the pathogenesis of colorectal neoplasms and their response to 5-FU treatment, paving the way for the identification of new therapeutic approaches for this type of cancer.

DECLARATIONS

Acknowledgments

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Ethical approval

The ethical protocol of this study was approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (ethical code: IR.UMSHA. REC.1401.485).

Consent to participate

Written informed consents were obtained from all participants.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

PM: designed the experiments, performed the data analyses, and contributed to the writing the manuscript; AM, RN, MH: designed the research, contributed to writing the manuscript; LT: performed the data analyses and contributed to writing the manuscript; SA: designed the research, obtained funding, and supervised the study.

Data availability

The data generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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