Proceedings of Anticancer Research, 2026, Volume 10, Issue 3
http://ojs.bbwpublisher.com/index.php/PAR
Online ISSN: 2208-3553
Print ISSN: 2208-3545

Lidocaine Regulates the Proliferation and Apoptosis of Colorectal Cancer Cells by Modulating AKR1B1/miR-21-5p Pathway

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Abstract: This study was to investigate the effect of lidocaine on the proliferation and apoptosis of the human colorectal carcinoma cell line (HCT116) and explore the underlying mechanism. HCT116 cells' proliferation and apoptosis rate were determined by CCK8 assay and flow cytometry, followed by treating the cells with 0.5 mM and 1 mM lidocaine. HCT116 cells were transfected with NC-mimic, Mimic-miR-21-5p, inhibitor-NC, and Inhibitor-miR-21-5p, followed by treatment with Lidocaine and fidarestat, combined and both alone. The expression of miR-21-5p and of AKR1B1, PTEN, p-AKT, AKT, and PI3K proteins was determined by qRT-PCR and Western blot. This study find lidocaine inhibited cell proliferation and promoted apoptosis in a time-dose dependent manner. Lidocaine and fidarestat, both alone and in combination, reduced the expression of miR-21-5p and AKR1B1. Lidocaine and fidarestat alone and combined treatments and the miR-21-5p-inhibitor group decreased the expression of p-AKT and PI3K and vice versa in the mimic-miR-21-5p group. The expression of PTEN was increased in the lidocaine + fidarestat group, decreased in the mimic-miR-21-5p group. These results suggest that lidocaine inhibited the proliferation of HCT116 cells and promoted cell apoptosis by downregulating the expression of AKR1B1/miR-21-5p and further modulating the PTEN/AKT/PI3K signaling pathway.

Keywords: Colorectal cancer; Lidocaine; Cell proliferation; Apoptosis; miR-21-5p; AKR1B1

Online publication: May 31, 2026

1. Introduction

Colorectal cancer (CRC) is a common tumor of the digestive tract. Globally, it is the third most common cancer type in males, while it ranks second in females [1]. Nowadays, it is a common emerging cancer among the Chinese population [2]. Generally, CRC is treated surgically and combined with chemotherapy and targeted treatment [3]. However, tumor recurrence and metastasis have been reported in many patients after

CRC surgery, hence minimization of tumor recurrence and metastasis incidents in patients after surgery is a challenging task for effective treatment of CRC. An effective treatment approach could help improve the prognosis and reduce the mortality rate of CRC patients. In clinical practices, lidocaine is a commonly used local anesthetic and antiarrhythmic drug [4]. Many studies have shown that lidocaine has an obvious anti-tumor effect and can effectively inhibit the proliferation and invasion of tumor cells, and thus could improve the disease-free survival outcome of tumor patients after surgery [5–8].

The occurrence and development of CRC is a complex process of multifactorial, multi-stage, multi-step, and multi-gene changes based on the molecular basis of oncogene activation and tumor suppressor gene inactivation. MicroRNAs (miRNAs) are closely related to tumors and can be used as oncogenes or tumor suppressor genes to regulate the occurrence, development, and metastasis of tumors [9, 10]. As a widespread miRNA, aberrant expression of miR-21-5p has been detected in a variety of cancers [11]. The human miR-21-5p gene is located in the fragile region of FRA17B on chromosome 17q23.2, which is a fragile site for multiple tumorigenesis. MiR-21-5p can combine with its target gene PTEN, inhibit its expression, widely participate in the regulation of various biological processes of the body, and play an important role as an 'oncogene' in tumorigenesis [12]. The abundance of miR-21-5p is high, and the changes are stable. Considering the increasing interest in exploring the function and mechanism of miR-21-5p in tumors, we chose miR-21-5p as the research observation index in the present study.

Lidocaine inhibits CRC cell proliferation and promotes cell apoptosis by upregulating the expression of miR-520a-3p [13]. Moreover, it inhibits the proliferation, migration, and invasion of lung cancer cells, as well as induces cell apoptosis by downregulating the expression of miR-21-5p [14]. However, the mechanism for the regulation of miR-21-5p needs to be further explored. Aldose keto reductase family 1 and member B1 (AKR1B1) [15]O, which catalyzes the reaction of glucose to sorbitol, can be used as a potential marker for tumor detection in lung cancer cells. In various malignant tumors, including CRC, the abnormal expression of AKR1B1 suggests its potential use as a marker for tumor detection as well as a therapeutic agent. Some studies have found that AKR1B1 is overexpressed during the development of CRC, and inhibiting its expression can prevent the growth of CRC cells induced by the growth factors through down-regulation of miR-21 expression [16,17]. In this study, we suggested the role of miR-21-5p in the prognosis of CRC; however, its regulatory mechanism induced by CRC needs further exploration.

The present study aims to investigate the effect of lidocaine on the proliferation and apoptosis of the human colorectal carcinoma cell line (HCT116) and explore the underlying mechanism. The cells were treated with lidocaine both alone and in combination with the aldose reductase inhibitor 'fidarestat', and their effect on cell proliferation and apoptosis was determined *in vitro*. The effective inhibition of growth and induction of apoptosis of colorectal cancer HCT116 cells by lidocaine indicates its effectiveness in treating CRC.

2. Methods

2.1. Cell Culture

HCT116 cells obtained from Shanghai Zhongqiao Xinzhou Biotechnology Co., Ltd. were used as the study material. Human colorectal carcinoma cells (HCT116) were cultured in DMEM medium (L110, Shanghai BasalMedia Technologies Co., LTD.-Shanghai) containing 10% Fetal Bovine Serum (FBS) (1803122, Biological Industries-Israel) and 1% penicillin/streptomycin (P/S) antibiotics (15070063, Thermo Fisher) and

incubated at 37 ℃ in a 5% CO_2 incubator (51020241, Thermo Fisher Scientific, USA).

2.2. CCK8 assay

HCT116 cells were digested by trypsin (S330JV, Shanghai BasalMedia Technologies Co., LTD), and a 100 μl solution containing 5 × 10^3 cells was cultured in a 96-well culture plate and incubated at 37 ℃ in a 5% CO_2 incubator for 24 h. In parallel, the cells treated with 0 mM, 0.5 mM, 1 mM, 2 mM, 5 mM, and 10 mM lidocaine were incubated for 48 h to determine the effect of different concentrations of lidocaine. Likewise, different concentrations (0 μM, 0.001 μM, 0.01 μM, 0.1 μM, 1 μM, 10 μM, 100 μM, 200 μM, and 500 μM) of fidarestat (HY-105185, MCE) were used to treat HCT116 cells for 48 h to explore the effect of different concentrations. The final volume of each well was maintained at 100 μL, and each drug concentration was set in 3 multiple wells, and the culture plate was incubated at 37 ℃. At 48 h, the reaction was stopped and the cell survival rate was determined. The optical density (OD) of the control and treated samples was measured at 450 nm wavelength by using a multifunctional microplate reader (SpectraMax M2e, Molecular Devices, USA).

2.3. Flow cytometry

HCT116 cells were treated with three different concentrations (0, 0.5, and 1 mM) of lidocaine and 100 μM fidarestat and incubated in a 96-well plate for 48 h. After incubation, the cells were digested with trypsin and counted. The cell density was adjusted to 1 with the staining buffer 1× 10^6/mL. Thereafter, Annexin V reagent (C1062S, Beyotime, China)) and PI were added to the mixture, mixed well, and incubated in the dark for 15 min before analysis *via* flow cytometry by using an inverted fluorescence microscope (OLYMPAS IX71, OLYMPAS, Japan) and FACS Calibur (BD Bioscience, USA).

2.4. Cell transfection

HCT116 cells were resuspended in DMEM medium containing 10% FBS in the absence of antibiotics. The cells were collected and seeded in a 6-well plate at a density of 5 × 10^4 cells/well, and incubated in a 5% CO_2 incubator at 37 ℃ for 24 h. After incubation, lipofectamine™ 2000 (11668-019, Invitrogen) was added for transfection, and the liposome 2000/RNA mixture was prepared. Different solutions were prepared as follows: Preparation of solution A: 5 μL miRNA (20 μM) dissolved in 50 μL serum-free 1640 medium; Preparation of solution B: transfer 5 μL liposome 2000 dissolved in 50 μL serum-free 1640 medium, incubate at room temperature for 5 min. Solutions A and B were mixed and placed at room temperature for 20 min. In parallel, 0.2 mL of the original cell culture solution was placed in the culture plate and the mixture of solution A and B was added drop-wise into the cell culture plate. The mixture was incubated in a 5% CO_2 incubator at 37 ℃ for 48 h. The mixture was replenished with fresh culture medium after sampling for analysis.

Grouping: control, mimic-NC, mimic-miR-21-5p, inhibitor-NC, inhibitor-miR-21-5p, lidocaine (0.5 mM), fidarestat (100 μM), lidocaine (0.5 mM) + fidarestat (100 μM). The miRNA was transfected for 48 h, and the drug acted for 48 h.

2.5. Quantitative real-time polymerase chain reaction

After each treatment, total RNA was extracted from HCT116 cells and the control group by using TRIzol reagent (15596026, Invitrogen, USA). cDNAs were synthesized using ReverTra Ace qPCR RT Kit (FSQ-101, TOYOBO). SYBR Green real-time PCR kit (4368708, Applied Biosystems) was used to carry out

qRT-PCR (ABI7500, ABI, USA). U6 was used as an internal standard to normalize the data. MiR-21-5p: primer sequence (5'-3'): F: TAGCTTATCAGACTGATGTTGAAAA, R: GTGCAGGGTCCGAGGT; U6 F: TTCGTGAAGCGTTCCATATTTT, R: GAATTTGCGTGTCATCCTTGC. The data was calculated using the $2^{-\Delta\Delta Ct}$ method.

2.6. Western blot

HCT116 cells were lysed with lysis buffer, and the total protein was quantified with the Bicinchoninic acid assay (BCA) kit (Sangon Biotech). The blots were incubated with primary antibody overnight at 4 ℃, AKR1B1 antibody (67498-1-Ig, Proteintech), AKT antibody (60203-2-Ig, Proteintech), p-AKT antibody (05-802R, Millipore), PI3K antibody (34050, Cell Signaling), PTEN antibody (22034-1-AP, Proteintech), GAPDH antibody (60004-1-1, Proteintech), HRP-goat anti-mouse IgG (H+L) (A0216, Beyotime biotechnology), and HRP-goat anti-rabbit IgG (H+L) (A0208, Beyotime Biotechnology) antibodies were used. TBST was washed three times, and then the secondary antibody was added and incubated at room temperature for 2 h. TBST was washed three times, and then the PVDF membrane was placed in PBS for 5 min. Thereafter, 200 μL of luminous solution (100 μL A solution + 100 μL B solution) was added for imaging, and then it was placed into the developer for developing the image after 2 min. ImageJ software was used to analyze the gray value of the strip.

2.7. Statistical analysis

The data were expressed as mean ± standard deviation (SD), and each experiment was performed in triplicate. Statistical software SPSS 22.0 was used for statistical analysis, and the analysis of variance was used for comparing the data among groups. The data was considered statistically significant at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

3. Results

3.1. Inhibition of proliferation of HCT116 cells by lidocaine in a dose-dependent manner

To evaluate the effect of lidocaine on the viability of cancer cells, the HCT116 cells were incubated in the presence of different concentrations of lidocaine for 48 h, and the results are shown in **Figure 1**. According to the cell viability results determined by CCK8 assay, the growth of HCT116 cells was significantly reduced after 48 h, even with 0.5 mM lidocaine treatment, as compared to the control group. Based on these results, the 0.5 mM and 1 mM concentrations of lidocaine and a treatment for 48 h were subsequently selected for determining its effect on the apoptosis of HCT116 cells and a mechanism study through qRT-PCR and Western Blot analysis.

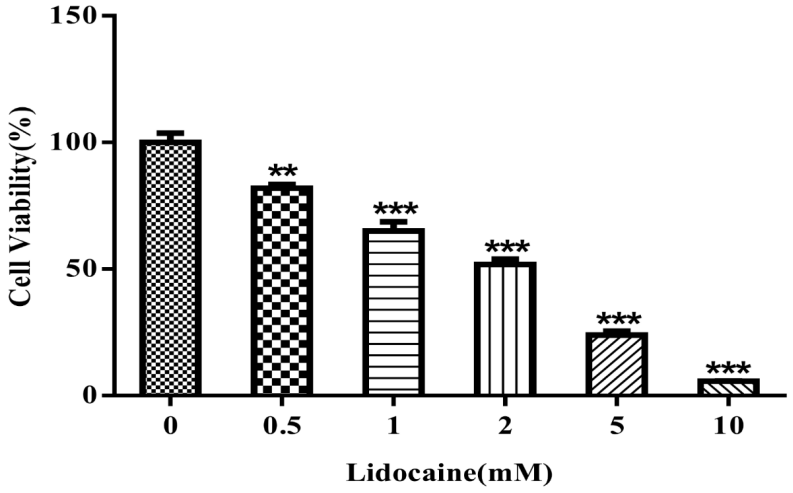

Figure 1. Effect of lidocaine on viability of HCT116 cell proliferation after 48 h.**$p < 0.01$ *vs.* 0 mM; ***$p < 0.001$ vs. 0 mM.

3.2. Induction of apoptosis of HCT116 cells by fidarestat

To explore the effect of fidarestat on cell viability, the HCT116 cells were treated with different concentrations (0 μM, 0.001 μM, 0.01 μM, 0.1 μM, 1 μM, 10 μM, 100 μM, 200 μM, and 500 μM) of fidarestat for 48 h. The cell viability analysis of the control and fidarestat-treated cells after 48 h showed that fidarestat significantly reduced the cell proliferation (**Figure 2**). The significant results ($^{***}p < 0.001$) were obtained at 100 μM and higher concentrations; hence, cells treated with 100 μM were used for subsequent analysis.

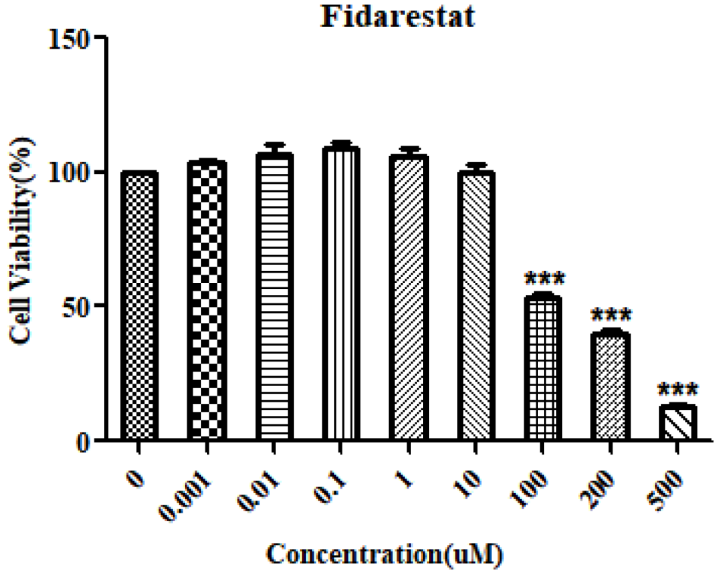

Figure 2. Effect of fidarestat on the proliferation of HCT116 cells after 48 h.$^{***}p < 0.001$ *vs.* 0 μM.

3.3. Lidocaine-induced apoptosis of HCT116 cells

The influence of lidocaine on cell apoptosis was determined by treating the HCT116 cells with 0.5 mM and 1 mM lidocaine for 48 h. The apoptosis rate was calculated based on the cytometry analysis. According to the results, lidocaine not only inhibited cell proliferation but also induced the process of cell death, which led to apoptosis. The highest apoptosis rate was observed upon treatment with 1 mM lidocaine (*$p > 0.05$), while no significant change was observed for 0.5 mM lidocaine treatment (**Figure 3A** and **B**).

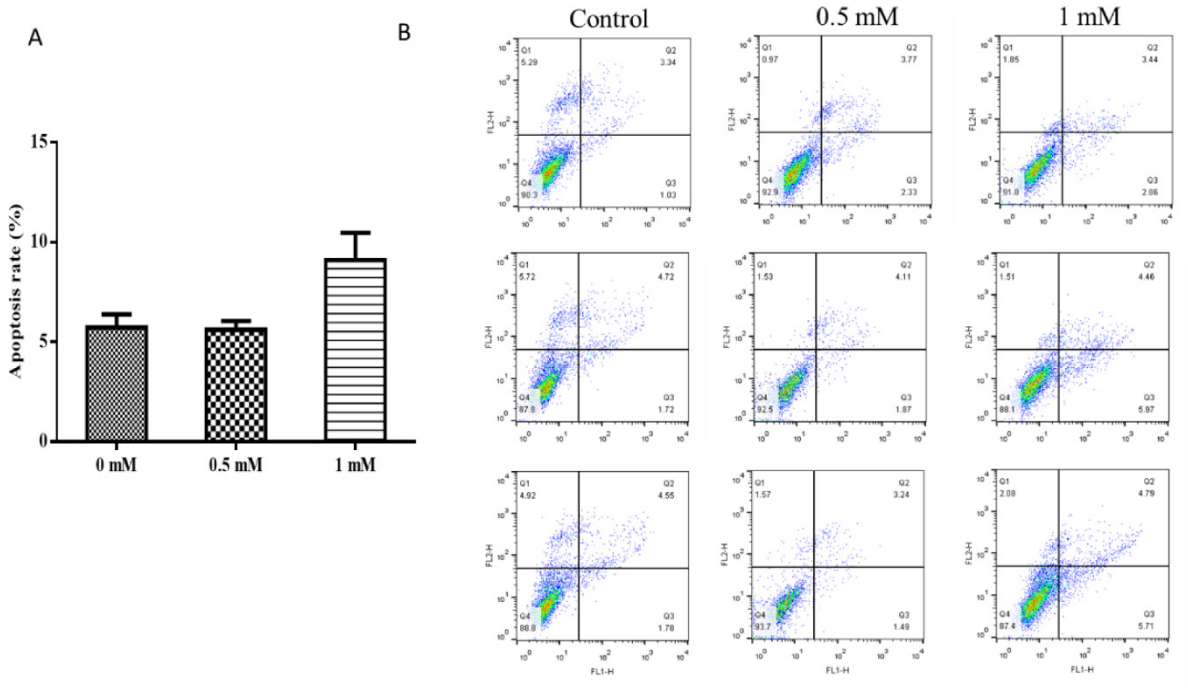

Figure 3. (A) Quantitative and (B) qualitative determination of the effect of lidocaine on apoptosis of HCT116 cells after treatment for 48 h.

3.4. Lidocaine decreased the expression of miR-21-5p in HCT116 cells

To investigate the association between miR-21-5p and lidocaine action on the CRC cells, HCT116 cells were transfected with miR-21-5p mimics and inhibitors, respectively. Compared to the control group, the expression of miR-21-5p in the transfected group was significantly higher ($^{**}p < 0.01$, **Figure 4**), and the expression of miR-21-5p in the miR-21-5p inhibitor group was significantly lower ($^{***}p < 0.001$). Moreover, the expression of miR-21-5p was examined in lidocaine, fidarestat, and combined lidocaine + fidarestat treatment groups. Results showed a decreased expression of miR-21-5p in the lidocaine (0.5 mM) group, and in addition, miR-21-5p expression was significantly decreased in the fidarestat group (100 μM). The expression of miR-21-5p in the combined lidocaine (0.5 mM) + fidarestat (100 μM) group was also significantly decreased ($^{***}p < 0.001$), suggesting that miR-21-5p may play an important role in CRC cell proliferation.

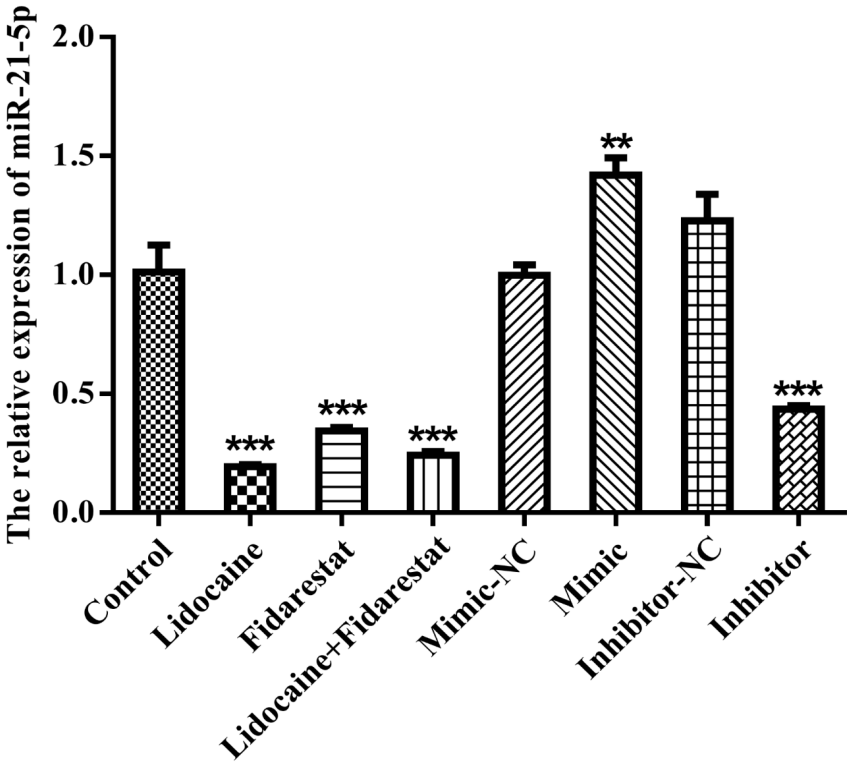

Figure 4. Expression level of miR-21-5p detected by qRT-PCR. $^{**}p < 0.01$ *vs.* Control; $^{***}p < 0.001$ *vs.* Control.

3.5. Lidocaine decreases the expression of AKR1B1 and regulates the PTEN-PI3K-AKT signaling pathway in CRC

To investigate the effect of lidocaine, fidarestat, and miR-21-5p mimic on the expression of AKR1B1, AKT, p-AKT, PI3K, and PTEN proteins, their expressions were measured through Western blot (**Figure 5A**). The relative expression of all proteins was analyzed and presented in **Figure 5B–F**. The expression results show that the expression of AKR1B1 was significantly decreased after lidocaine and fidarestat treatment. The decreased expression after both alone and combined lidocaine + fidarestat treatment was also noticed ($^{**}p < 0.01$ or $^{***}p < 0.001$) (**Figure 5B**). Whereas no significant change in the expression level of AKR1B1 was noticed in miR-21 mimic and inhibitor-transfected cells ($p > 0.05$) compared to the control. The results did not show a significant difference in the expression of AKT in both the mimic and inhibitor groups of miR-21-5p. A slight increase in the mimic group, while a minor decrease in the inhibitor group was noticed as compared to their respective control groups (**Figure 5C**). The expression of p-AKT (**Figure 5D**) and PI3K (**Figure 5E**) was significantly increased ($^{***}p < 0.001$) in the mimic-miR-21-5p group, and low values were obtained after lidocaine and fidarestat alone and combined treatments ($^{***}p < 0.001$). The low expression of p-AKT and PI3K was also recorded in miR-21-5p inhibitor-transfected cells. The mimic-transfected cells showed low expression of PTEN, while cells transfected with miR-21-5p inhibitor showed high PTEN expression compared to the control group (**Figure 5F**). The high expression of PTEN was noticed after lidocaine and fidarestat combined treatment. These results suggest a major role of miR-21-5p in AKR1B1 expression and regulation of the PTEN-PI3K-AKT signaling pathway in CRC.

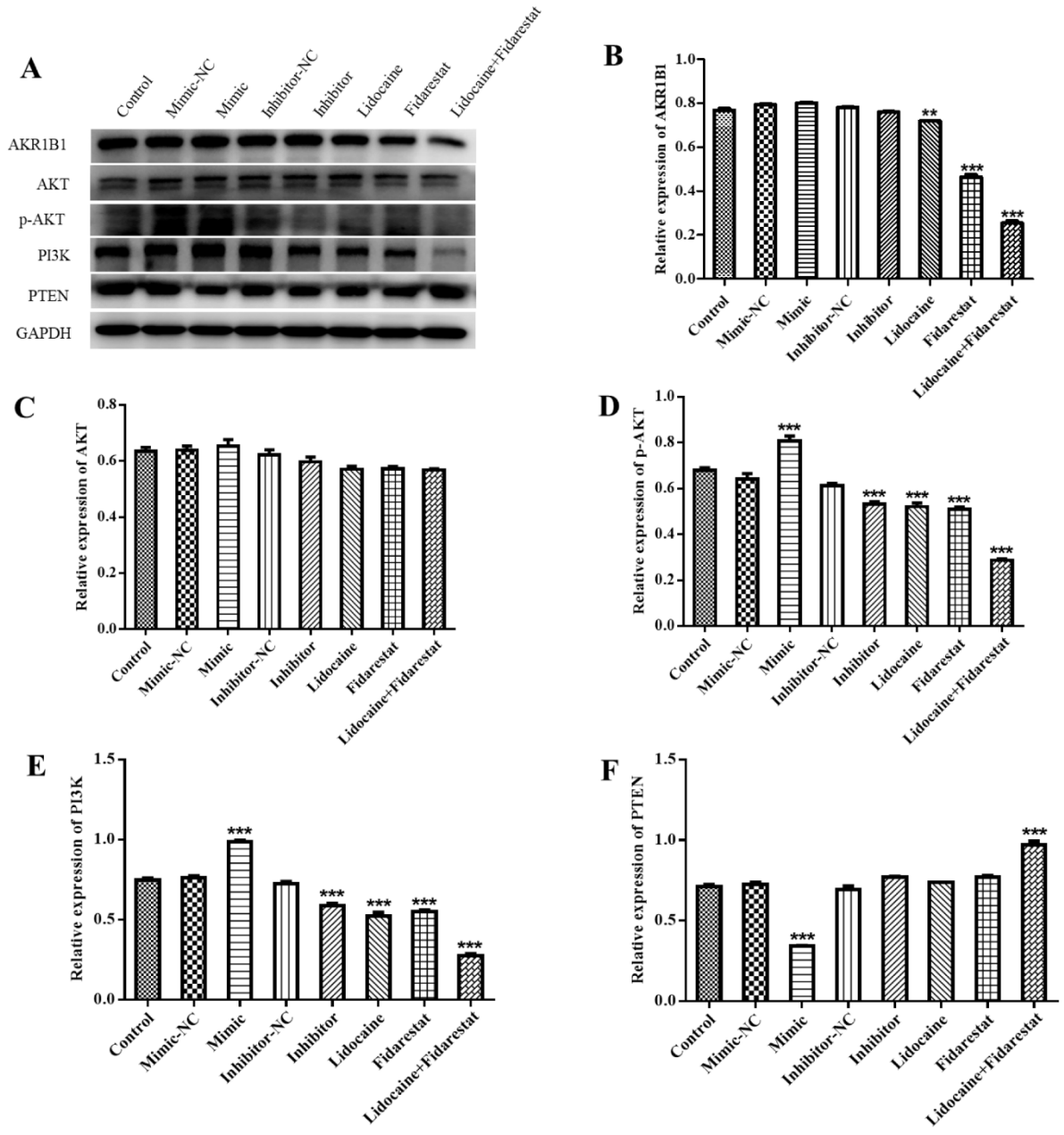

Figure 5. Western blot analysis of protein expression level.(A) Western Blot analysis, (B) AKR1B1 gray quantification, (C) AKT quantification, (D) P-AKT gray quantification, (E) PI3K gray quantification, and (F) PTEN gray quantification.**$p< 0.01$ *vs.* Control; ***$p< 0.001$ *vs.* Control

4. Discussion

In the present study, lidocaine treatment effectively inhibited the proliferation of HCT116 cells in a dose-dependent manner, with 0.5 mM and 0.1 mM lidocaine found effective for inhibiting cell proliferation. Moreover, lidocaine promoted cell apoptosis by downregulating the expression of AKR1B1/miR-21-5p and

further modulated the PTEN/AKT/PI3K signaling pathway. Interestingly, a combined treatment of HCT116 cells with lidocaine and fidarestat showed a synergistic apoptotic effect, indicating their usefulness in treating CRC.

Lidocaine tends to inhibit cancerous cell growth and spread, especially in CRC. The findings of the present study are consistent with previous studies that showed the negative effect of lidocaine on lung cancer cells' viability by downregulating the expression of miR-21-5p [14]. Another study suggested that lidocaine upregulated the expression of miR-520a-3p and inhibited CRC cell proliferation and induced cell death [13]. Lidocaine also controls the miR-1204 expression and prevents CRC occurrence [18]. This study reports the effect of lidocaine on miR-21-5p expression in CRC. Lidocaine significantly inhibited the expression of miR-21-5p and the expression of PI3K, p-Akt proteins. It was found that the apoptosis of HCT116 cells was significantly increased after 1 mM lidocaine treatment; however, there was no statistical significance, which may be related to the relatively small concentration of lidocaine used. Studies have shown that the concentration of lidocaine in promoting apoptosis in gastric cancer [19,20], breast cancer [21], lung cancer [22], and other cancer cells was higher than 1 mM [23,24]. Our findings validate the involvement of miR-21-5p in regulating the downstream PTEN/PI3K/AKT signaling pathway, which was previously identified by Yang et al. [25]. This signaling network is critical for CRC progression and prognosis. This study found that after HCT116 cells were transfected with mimic-miR-21-5p, the expression level of PTEN was significantly reduced, and the expression level of PI3K and p-AKT was significantly increased. However, after treatment with miR-21-5p inhibitors, the expression level of PTEN did not change much, and the expression of p-AKT and PI3K was significantly decreased. The changing trend was basically consistent with that of Yang et al. [25]

AKR1B1 is an NADPH-dependent monomer enzyme and also a rate-limiting enzyme in the polyol pathway of glucose metabolism [26]. It has been widely studied due to its important role in the occurrence and development of diabetes complications and various oxidative stress diseases [26]. In recent years, studies have found that AKR1B1 was overexpressed in various forms of malignant tumors [27,28], which can lead to cancer cell metastasis, adhesion, invasion, and migration [29]. It has been reported that inhibition of aldose reductase can prevent the growth of colon cancer cells induced by the growth factors by down-regulating the expression of miR-21 expression [17]. These studies suggested that aldose reductase may be a potential tumor marker and a new therapeutic target for CRC. In addition, the aldose reductase inhibitor, fidarestat, can improve the sensitivity of doxorubicin to CRC cells and reduce its cardiotoxicity [30]. This study found that both fidarestat and lidocaine can inhibit the proliferation of CRC cells and reduce the expression level of microRNA-21. The expression level of PTEN increased while that of PI3K and p-AKT decreased after a combination of lidocaine and fidarestat. These results indicate that there were similarities in the anti-tumor mechanism between lidocaine and fidarestat in CRC. Moreover, this study also found that lidocaine inhibited the expression of AKR1B1, suggesting that the anti-tumor effect of lidocaine may be related to the inhibition of aldose reductase, and its specific mechanism needs to be further explored.

5. Conclusion

In summary, this study showed that lidocaine inhibits the proliferation of HCT116 and promotes its apoptosis by downregulating AKR1B1/miR-21-5p, which ultimately controls PTEN/PI3K/AKT expression in CRC. This study provides an experimental basis for the application of lidocaine in the perioperative period of CRC, and also provides a new reference for lidocaine to become an ideal anesthetic in the surgical treatment

of CRC, to improve the prognosis of CRC patients. The impact of lidocaine on aldo reductase-miR-21-5p expression and related pathway was identified for the first time in CRC. However, there is still a need to identify other target elements and regulating factors that are involved downstream in this pathway. The identification of the regulatory network associated with miR-21-5p can be further carried out in future studies to better understand the underlying mechanism.

Funding

Huaian Science and Technology Project Fund (Project No.: HAB202317)

Disclosure statement

The authors declare no conflict of interest.

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