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Adrenaline promotes cell proliferation and increases chemoresistance in colon cancer HT29 cells through induction of miR-155

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ABSTRACT

Recently, catecholamines have been described as being involved in the regulation of cancer genesis and progression. Here, we reported that adrenaline increased the cell proliferation and decreased the cisplatin induced apoptosis in HT29 cells. Further study found that adrenaline increased miR-155 expression in an NFκB dependent manner. HT29 cells overexpressing miR-155 had a higher cell growth rate and more resistance to cisplatin induced apoptosis. In contrast, HT29 cells overexpressing miR-155 inhibitor displayed decreased cell proliferation and sensitivity to cisplatin induced cell death. In summary, our study here revealed that adrenaline–NFκB–miR-155 pathway at least partially contributes to the psychological stress induced proliferation and chemoresistance in HT29 cells, shedding light on increasing the therapeutic strategies of cancer chemotherapy.

1. Introduction

Colon cancer is one of the most common cancers worldwide, causing nearly half a million deaths each year [1]. Chemoresistance is one of the biggest problems in colorectal cancer therapy, and elucidating the underlying mechanism would improve the prognosis. Recently, catecholamines are found to be involved in the regulation of cancer genesis and progression in many cancer types, such as breast cancer, lung cancer and pancreatic cancer [2,3]. Catecholamines are reported to enhance the carcinogenic effect of tobacco-specific nitrosamine as was indicated by the development of pulmonary adenocarcinoma in hamsters [2]. In addition, chronic elevation of adrenaline and noradrenaline has been found in the plasma and urine of breast cancer patients [4], and β-adrenergic receptors have been characterized in human breast cancer cells [3].

The human colon is particularly sensitive to stress because of the close distribution of noradrenergic fibers to its basement lamina [5], In addition, colorectal cancer cells are found to express adrenergic receptors [6]. Mice model experiments showed that psychological stress, which produces catecholamine signals, was found to reduce the antitumor effects of chemotherapeutic drugs [7]. Also, psychological stress has also been implicated in cancer metastasis to the liver [8,9]. Very recently, adrenaline was found to induce multidrug resistance in colon cancer cells by upregulating ABCB1 gene expression in HT29 cells [6]. However, the underlying mechanism of how adrenaline induces chemoresistance remains largely unknown.

miRNAs are an abundant class of 19–22 nucleotide-long, non-coding RNAs, with a primary role in the post-transcriptional triggering of messenger RNA degradation or translational repression through binding to the 3′-untranslated region (UTR) of protein-coding transcripts [10]. Although miR-155 was found to be uniquely expressed in the activated cells of immune system and lymphomas, miR-155 is also found to be highly expressed in colon cancer [11–14] and play an oncogenic role.

miR-155 has been found to promote cell proliferation, migration and inhibit cell apoptosis in colon cancer cells [15]. On the other hand, miR-155 is upregulated by NFκB [16], while adrenaline has been found to increase the NFκB activity in both hepatic stellate cells and monocytes [17,18]. Taken together, this information suggests that adrenaline might function through regulating the expression of miR-155. Our study here was to investigate the effects of adrenergic activation on the cell proliferation and chemoresistance of colon cancers, and to explore the role of miR-155 in this process.

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2. Materials and methods

2.1. Cell culture

Colorectal cancer cells HT29 (ATCC) were cultured in 1640 medium (Invitrogen), supplemented with 2 mM glutamine, 0.06 g/l penicillin, 0.1 g/l streptomycin and 10% fetal bovine serum (FBS) (Sijiqing, Hangzhou, China) at 37 °C in a humidified atmosphere of 5% CO_2. Adrenaline- (adrenaline bitartrate; Sigma–Aldrich, Munich, Germany) was added to the medium at various concentrations for indicated times. For the treatment of cisplatin, cells were pretreated with ascorbic acid, which prevents adrenaline oxidation. NFκB inhibitor BAY 11-7082 (10 μM) was added 3 h prior to the adrenaline treatment in indicated groups.

2.2. miR-155 expression analysis

RNA was isolated with an RNA Mini Kit (Invitrogen) according to the manufacturer's protocol, and reverse transcribed with the Qiagen miRNA reverse transcriptase kit. The subsequent PCR reaction was carried out in a 25 μL system using SYBR Green kit with the miR-155 specific forward primer (Table 1) and universal downward primer. U6B served as an internal control. Relative expression of miR-155 was calculated using the $2^{-\Delta\Delta Ct}$ method.

2.3. Synthesis and transfection of miR-155 mimic and miR-155 inhibitor

Negative control, or miR-155 mimics, or the single strand miR-155 inhibitor were synthesized in Shanghai Genepharm, with the sequences indicated in Table 1. Transfection of these RNAi duplexes was done using Lipofectamine2000. After recovery for 12 h, cells underwent further treatment.

Table 1
Sequences used in this study.

Name	sequence
NC siRNA	5′-UUCUCCGAACGUGUCACGUTT-3′ 5′-ACGUGACACGUUCGGAGAATT-3′
miR-155 mimic	5′-UUAAUGCUAAUCGUGAUAGGGGU-3′ 5′-CCCUAUCACGAUUAGCAUUAATT-3′
miR-155 inhibitor	5′-CCCUAUCACGAUUAGCAUUAATT-3′
NC inhibitor	5′-UUCUCCGAACGUGUCACGUTT -3′
miR-155 forward primer	5′-TTAATGCTAATCGTGATAGGGGT-3′

2.4. MTT assay

To assess cell proliferation and survival, an MTT test was included. Briefly, cells with different treatments were seeded at a density of 1000 or 10,000 cells/well in 96-well plates. 3-(4,5-methylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, SigmaeAldrich, Germany) was added (100 μg/well) at the indicated time, and 4 h later the cell culture medium was removed. Formazan products were solubilized with DMSO, and the optical density was measured at 490 nm. All experiments were performed in triplicate.

2.5. Western blot assay

Cells with indicated treatments were washed twice with ice-cold PBS and lysed with whole cell lysis buffer or cytoplasmic and nuclear subfraction lysis buffer (Promega). Protein concentration was determined by the BCA protein assay (Pierce Chemical Co., Rockford, IL, USA). Equal amounts of cell lysates were run on SDS polyacrylamide gels and transfered onto nitrocellulose membranes. Membranes were then incubated in blocking solution (5% nonfat-milk in 20 mM Tris–HCl, 150 mM NaCl, 0.1% Tween-20) (TBS-T), followed by incubation with the indicated antibodies (p65, caspase-3, lamin B, PPP2CA or β-actin) at 4 °C overnight.

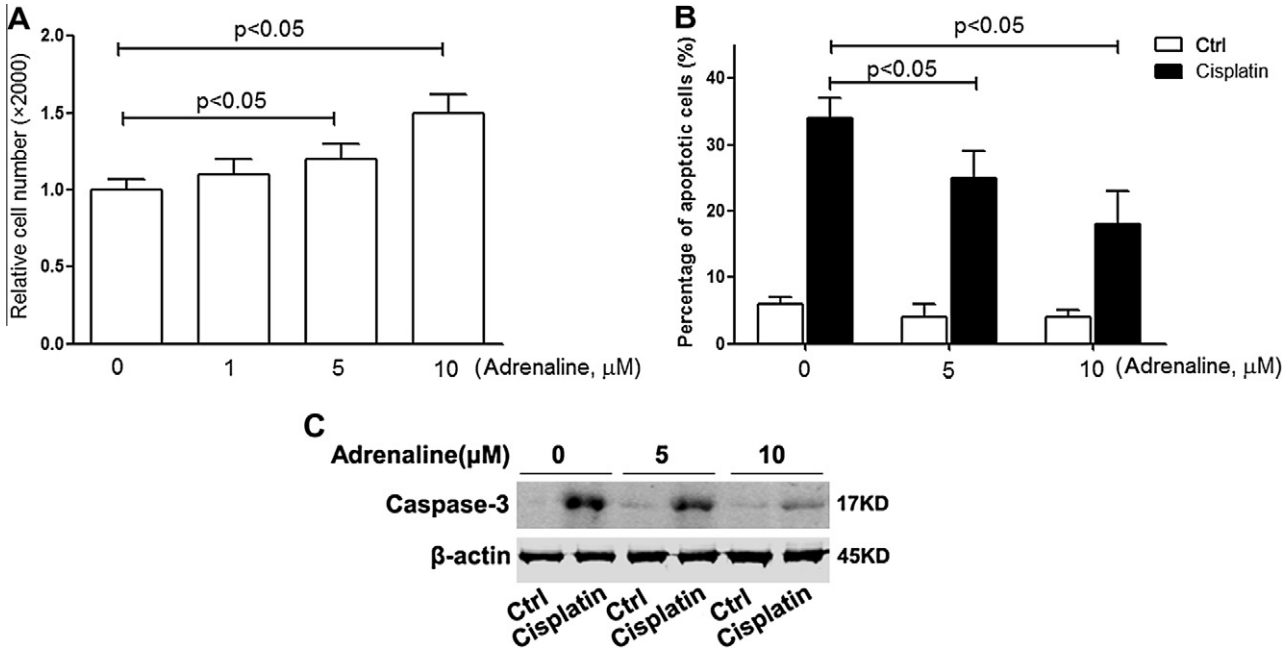

Fig. 1. Adrenaline increased cell proliferation and resistance to cisplatin. (A) Adrenaline increased the cell proliferation of HT29 cells. HT29 cells were treated with 0, 1, 5, and 10 μM adrenaline for 24 h before harvest for survival cell number calculation by MTT. All the experiments were done in triplicate. (B) Adrenaline reduced the sensitivity of HT29 cells to chemotherapy. Cells were treated with 0, 5 or 10 μM adrenaline 24 h before 50 μM cisplatin treatment. Apoptosis was analyzed by FACS and expressed as the percentage of apoptotic cells. All the experiments were done in triplicate. $^{*}p < 0.05$. (C) Cells were treated same as above and apoptosis was analyzed by Western blot against the caspase-3. Data presented is a representative of three different experiments.

The membranes were then washed in TBS-T and incubated with HRPO-conjugated secondary antibodies for 1 h at room temperature. Antibody detection was performed with an enhanced chemiluminescence reaction.

2.6. NFκB activity examination

Cells were plated into 24-well plates at a density of 70% confluence at the time of transfection. Cells were transiently transfected in triplicate with 3× κB reporter vector and pRL-TK vector by Lipofectamine 2000 (Invitrogen). Six hours later, cells were removed with fresh medium and treated with a drenaline or NFκB inhibitor BAY 11-7082 (10 μM) or in combination. Cells were lysed using passive lysis buffer and analyzed for firefly and Renilla luciferase activities using the dual luciferase reagent assay kit (Promega) according to the manufacturer's instructions. Data were expressed as means ± SD of at least three independent experiments. Statistical analysis was performed using Student's *t* test. A value of $p < 0.05$ was considered as significant difference.

2.7. FACS analysis

To determine whether cell death was attributable to apoptosis, whole cells were stained with FITC-conjugated Annexin V (BD Pharmingen™) and PI (in PBS) according to the manufacturer's protocol. All analyses of whole cells were performed using appropriate scatter gates to exclude cellular debris and aggregated cells.

3. Results

3.1. Adrenaline increased cell proliferation and resistance to cisplatin

To explore the effects of adrenaline on colon cancer cells, we first analyzed the cell proliferation of HT29 cells upon adrenaline

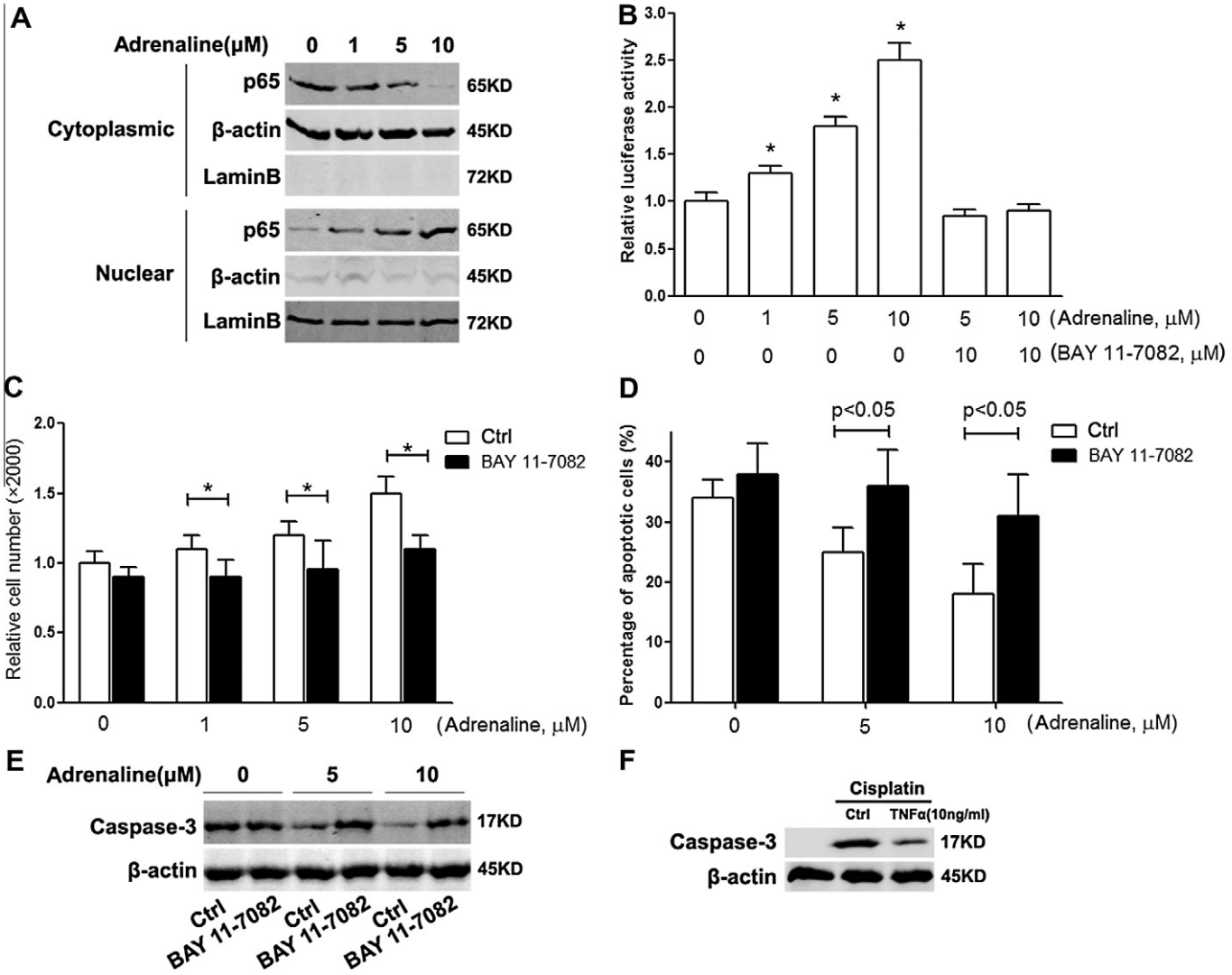

Fig. 2. Adrenaline activated NFκB in a dose dependent manner. (A) Adrenaline promotes p65 nuclear localziation in a dose dependent manner. HT29 cells were treated with indicated doses of adrenaline. Subcellular p65 was analyzed by Western blot. Date presented is a representative of three different experiments. (B) Adrenaline activated NFκB in a dose dependent manner. HT29 cells were transfected with NFκB activity reporter before indicated treatment. NFκB activity was calculated based on the relative luciferase activity. All the experiments were done in triplicate. $^{*}p < 0.05$ versus control. (C) Inhibition of NFκB blocked the effects of adrenaline on cell proliferation. Prior to adrenaline stimulation, pretreatment of NFκB inhibitor BAY 11-7082 (10 μM) significantly reduced the cell proliferation. (D) Inhibition of NFκB blocked the effects of adrenaline on chemoresistance. Prior to adrenaline and cisplatin stimulation, pretreatment of NFκB inhibitor BAY 11-7082 (10 μM) significantly reduced the cell proliferation and chemoresistance. (E) Cells were treated same as above and apoptosis was analyzed by Western blot against the caspase-3. Data presented are a representative of three different experiments. (F) Cells were treated with cisplatin or in combination with TNFα. Cell apoptosis was analyzed by Western blot against the caspase-3. Data presented are a representative of three different experiments.

treatment. As shown in Fig. 1A, 24 h adrenaline treatment dose dependently increased the cell number from 1 μM to 10 μM. Besides the cell proliferation promoting role of adrenaline, either 5 μM or 10 μM adrenaline treatment also significantly decreased cisplatin induced apoptosis as seen both by the FACS analysis and cleaved caspase-3 (Fig. 1B and C).

3.2. Adrenaline activated NFκB in a dose dependent manner

Previous studies revealed that the catecholamine signal could activate the NFκB pathway in both hepatic stellate cells and monocytes [17,18], suggesting that adrenaline could also activate the NFκB pathway in colon cancer cells. A subcellular fraction assay revealed that adrenaline induced a dose dependent p65 nuclear localization (Fig. 2A). To further quantify the effect of adrenaline on NFκB activity in HT-29 cells, we treated the cultures with adrenaline for 24 h and measured the NFκB activity by means of a reporter assay. Adrenaline treatment significantly increased the NFκB activity in a dose dependent manner. Specific NFκB inhibitor BAY 11-7082 (10 μM) reduced the basal and adrenaline induced activation of NFκB (Fig. 2B). Consistent with the reduced NFκB activity, treatment of BAY 11-7082 (10 μM) significantly reduced the cell proliferation (Fig. 2C). A further study revealed that BAY 11-7082 also antagonized the adrenaline induced resistance to apoptosis upon cisplatin treatment (Fig. 2D and E). In contrast, TNFα, an activator of NFκB could mimic the role of adrenaline, reducing the apoptosis induced by cisplatin treatment (Fig. 2F). All of the above results suggest that NFκB plays a central role in adrenaline induced chemoresistance.

3.3. miR-155 contributes to increased cell proliferation and resistance to cisplatin under adrenaline treatment

From the above data, we could see that NFκB activation is essential for the effects of adrenaline on cell proliferation and chemoresistance. To further explore the underlying mechanism, we

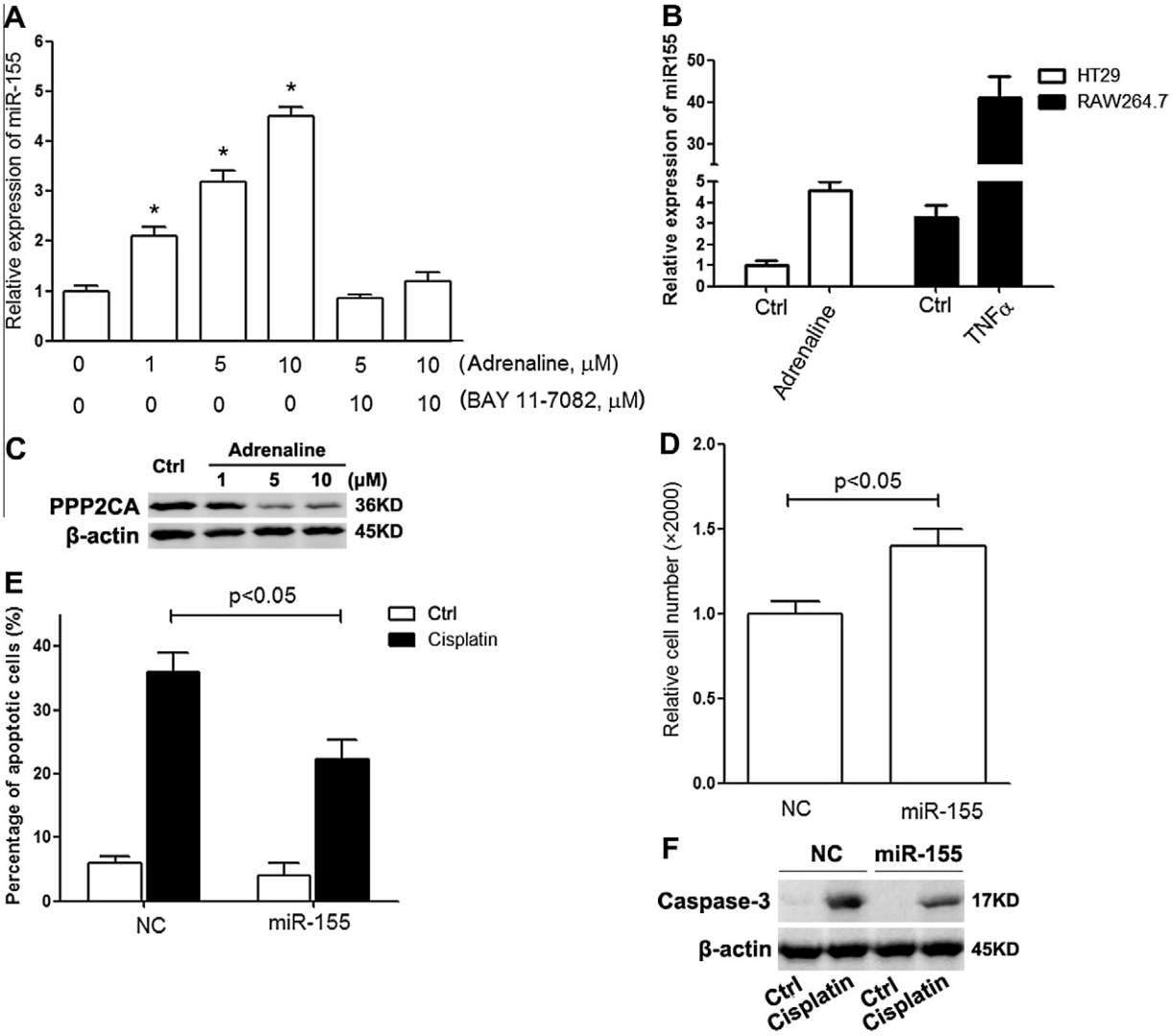

Fig. 3. Adrenaline treatment increased miR-155 expression in an NFκB dependent manner. (A) HT29 cells were treated with 0, 1, 5, and 10 μM adrenaline in the absence or presence of NFκB inhibitor BAY 11-7082 (10 μM) for 24 h before harvest for miR-155 expression. Expression of miR-155 was expressed as $2^{-\Delta\Delta Ct}$. All the experiments were done in triplicate. $^{*}p < 0.05$. (B) miR-155 expression in HT29 and RAW264.7 cells. HT29 and RAW264.7 cells were treated with adrenaline and TNFα respectively and miR-155 expression was determined by RT-PCR. (C) Expression of PPP2CA in HT29 cells treated with indicated concentrations of adrenaline. Expression of PPP2CA was analyzed by Western blot and data presented are a representative of three different experiments. (D) miR-155 expression increased the cell proliferation of HT29 cells. HT29 cells were treated with miR-155 mimic or NC RNA duplexes for 24 h before harvest for survival cell number calculation by MTT. All the experiments were done in triplicate. (E) miR-155 expression reduced the sensitivity of HT29 cells to chemotherapy. Cells were treated same as above and 24 later cells were additionally treated with 50 μM cisplatin for 24 h. Apoptosis was analyzed by FACS and expressed as the percentage of apoptotic cells. All the experiments were done in triplicate. $^{*}p < 0.05$. (F) Cells were treated same as above and apoptosis was analyzed by Western blot against the caspase-3. Data presented is a representative of three different experiments.

focused on the miRNAs regulated by NFκB. miR-155 is a well-known NFκB target, and has recently been found to be an oncogene [19]. As expected, adrenaline treatment dose dependently increased miR-155 expression, while inhibition of NFκB blocked the miR-155 induction (Fig. 3A). Previously, miR-155 was considered as a unique miRNA expressed in the activated immune cells. To this end, we further compared miR-155 expression in adrenaline treated cells with its expression in 10 ng/ml TNFα stimulated RAW264.7 cells. Although miR-155 expression adrenaline treated HT29 cells was about 5-fold lower than TNFα stimulated RAW264.7 cells, its expression was abundant in HT29 cells, suggesting its role in HT29 cells (Fig. 3B). Consistently, phosphatase protein phosphatase 2A catalytic subunit alpha (PPP2CA), the well-known target of miR-155 [12], was also suppressed by adrenaline (Fig. 3C), further suggesting miR-155 might play an important role in adrenaline induced cell proliferation and chemoresistance. Transfection of miR-155 mimic could partially mimic the effects of adrenaline on cell proliferation (Fig. 3D) and chemoresistance (Fig. 3E and F). In contrast, miR-155 inhibitor significantly blocked the effects of adrenaline on cell proliferation (Fig. 4A) and chemoresistance (Fig. 4B and C), similarly to NFκB inhibitor. Taken together, our data suggest that miR-155 is one of the key NFκB downstream molecules mediating the effects of adrenaline in HT29 cells.

4. Discussion

Our study here revealed that adrenaline could increase the cell proliferation and induce the cisplatin resistance by activation of the NFκB pathway and subsequent induction of miR-155.

Recently, psychological stress has been found to be involved in the genesis and progression of cancer. The altered pattern of neuronal or hormonal secretions during stress is considered to be the key factors. However, the underlying mechanism is as yet largely unknown. The study here will add novel insights into how psychological stress contributes to the genesis and progression of colon cancer. Catecholamines are one of the most important neuronal factors elevated under the psychological stress. In a recent survey, higher levels of depressive symptoms were found to be associated with greater numbers of aberrant crypt foci in patients at risk of colon cancer [20]. To this end, increased activation of NFκB pathway and the subsequent miR-155 would increase the cell proliferation and contributes to the initiation of colon cancer. Consistently, activated NFκB pathway and higher miR-155 expression were seen in many colorectal cancer patients [11]. Besides the initiation, the adrenaline–NFκB–miR-155 pathway might also involve in the acquired chemoresistance. Chemotherapy generates heightened psychological distress, which accompanied with chronic elevation of plasma catecholamines [21,22], in a significant number of colon cancer patients [23] while these patients inclined to display a poor prognosis [24]. In other words, increased NFκB and miR-155 might confer the drug resistance and poor response. It is highly possible that miR-155 promotes the cell proliferation and delivers the chemoresistance by targeting multiple downstream genes. miR-155 was found to promote the cell proliferation by targeting SRY-6 in hepatocellular carcinoma [25]. miR-155 was also found to target FOXO3a in breast cancer cells, which is responsible for the drug resistance [26]. Further testing these regulatory modules in our system and unraveling novel targets is now undergoing.

In summary, adrenaline stimulation contributes to the increased proliferation and chemoresistance in colon carcinoma cells via activation of NFκB and the subsequent enhancement of miR-155.These findings provide a molecular evidence to explain the adverse influence of catecholamines on cancer initiation, progression, and prognosis. Our results also indicate that targeting the adrenaline–NFκB–miR-155 pathway is a potential strategy for both cancer prevention and therapy.

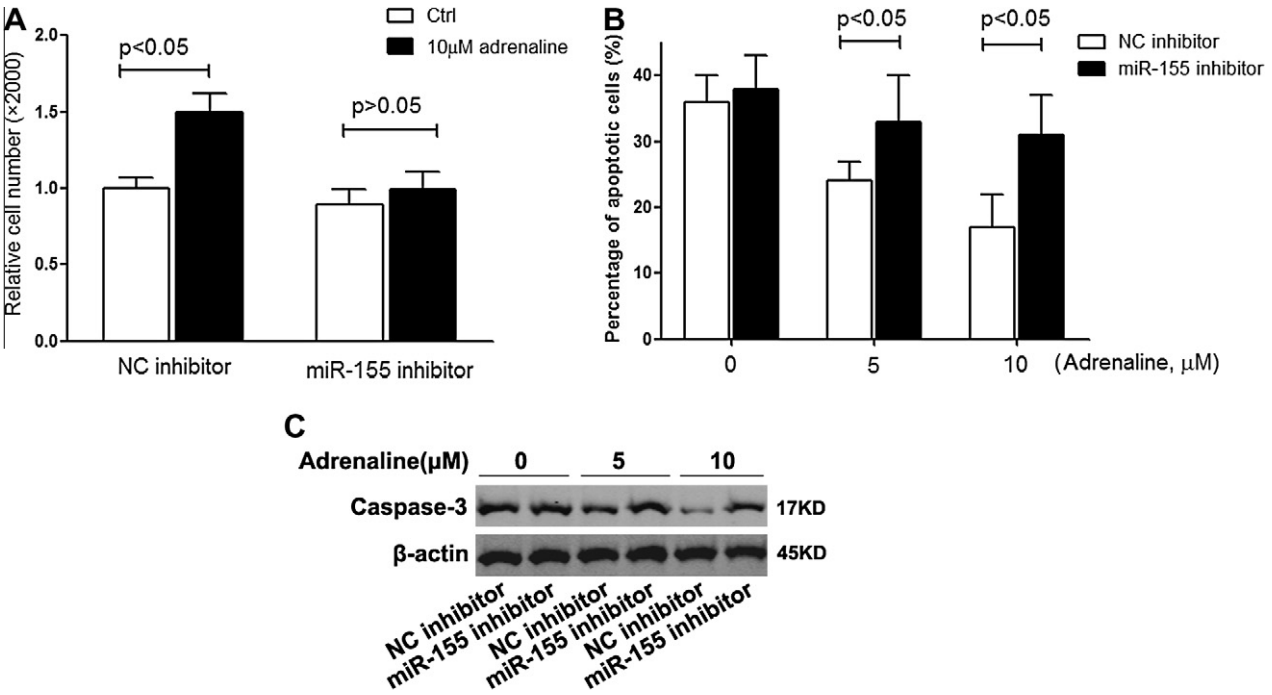

Fig. 4. miR-155 contributed to increased cell proliferation and chemoresistance under adrenaline treatment. (A) miR-155 inhibitor blocked the effects of adrenaline on cell proliferation. Transfection of miR-155 inhibitor significantly reduced the cell survival number. (B) miR-155 inhibitor blocked the effects of adrenaline on chemoresistance. Cells transfected with miR-155 inhibitor or control RNAi duplex were further treated with cisplatin or control. Apoptosis was analyzed by FACS. Transfection of miR-155 inhibitor significantly reduced the adrenaline induced chemoresistance. (C) Cells were treated same as above and apoptosis was analyzed by Western blot against the caspase-3. Data presented is a representative of three different experiments.

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