LncRNA KCNQ1OT1 is a key factor in the reversal effect of curcumin on cisplatin resistance in the colorectal cancer cells

Zhi-hai Zheng1,2 · He-yi You2 · Yu-jie Feng1 · Zhong-tao Zhang1

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Abstract
The development of cisplatin resistance is a common cause of cancer recurrence in colorectal cancer (CRC). Though many studies have reported the oncogenic function of long non-coding RNA (LncRNA) KCNQ1OT1 in multiple cancers, few studies explored its role in cisplatin resistance of CRC. Curcumin is a natural phenolic compound extracted from turmeric, which can effectively suppress cisplatin resistance in CRC. This study aims to expound the role of KCNQ1OT1 in cisplatin resistance in CRC cells and whether KCNQ1OT1 participates in the reversal effect of curcumin on cisplatin resistance in CRC. The interplay between KCNQ1OT1 and miR-497 was determined using RNA pull-down assay and dual-luciferase reporter gene assay. The combination of B-cell lymphoma 2 (Bcl-2) and miR-497 was confirmed using dual-luciferase reporter gene assay. Compared with CRC cell line HCT8, the cisplatin-resistant CRC cell line HCT8/DDP exhibited a higher expression level of KCNQ1OT1. Functionally, the silence of KCNQ1OT1 suppressed proliferation and boosted apoptosis in HCT8/DDP cells. Subsequently, we found that KCNQ1OT1 could act as a sponge of miR-497 and remove the suppressive effect of miR-497 on Bcl-2 expression. Curcumin treatment restrained proliferation and facilitated apoptosis in HCT8/DDP cells. While KCNQ1OT1 overexpression removed the effect of curcumin on HCT8/DDP cells via miR-497/Bcl-2 axis. Finally, the in vivo experiments showed that the inhibitory effect of curcumin on the growth of cisplatin-resistant CRC cells was reserved by the ectopic expression of KCNQ1OT1. In conclusion, KCNQ1OT1 aggravated cisplatin resistance in CRC cells via the miR-497/Bcl-2 axis. Administration of curcumin could effectively downregulate KCNQ1OT1 expression, thus reversing cisplatin resistance in CRC cells.

Keywords LncRNA KCNQ1OT1 · B-cell lymphoma 2 · Curcumin · Cisplatin resistance · Colorectal cancer

Introduction
Colorectal cancer (CRC) is the most common gastrointestinal malignancy and the third leading cause of cancer-related deaths worldwide [1]. Despite surgical resection combined with chemotherapeutic agents such as cisplatin achieve good treatment outcomes at the early stages. The development of cisplatin resistance after prolonged treatment is a common cause of cancer recurrence [2]. Therefore, clarifying the underlying mechanisms of cisplatin resistance has great significance for the clinical treatment of CRC.

B-cell lymphoma 2 (Bcl-2) is a key member of the proto-oncogene Bcl-2 protein family and responsible for the regulation of cell apoptosis [3]. Increasing evidence showed that Bcl-2 contributed to the development of cisplatin resistance in various cancers. For example, in non-small cell lung cancer, the elevation of the Bcl-2 level was associated with the cytoplasmic repressor/activator protein-1-mediated cisplatin resistance [4]. The Bcl-2 overexpression induced by paxillin conferred 5-fluorouracil resistance in CRC [5]. Notably, the Bcl-2 inhibitor YC137 synergized cisplatin sensitivity in nasopharyngeal carcinoma cells via suppressing Bcl-2 protein expression [6], indicating that Bcl-2 is a potential target to reverse the resistance to cisplatin in cancers.
In the last decade, several studies hypothesized that the occurrence of cancer is associated with the dysregulation of microRNAs (miRNAs), small non-coding RNAs that negatively regulate gene expression at the post-transcriptional level [7, 8]. Through CRC miRNAs profiling datasets analysis, Falzone et al. [9] screened out 19 miRNAs that were differentially expressed in CRC tissues. Among them, miR-497 was significantly down-regulated and its overexpression restrained the progression of CRC in vitro [10]. Besides, Zhu et al. [11] reported that miR-497 decreased cisplatin resistance in human lung cancer cell lines via targeting Bcl-2. Hence, it is reasonable to hypothesize that in CRC, miR-497 promoted the chemosensitivity of cells to cisplatin through modulating Bcl-2 expression.

Long non-coding RNA (LncRNA) KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) is located at the KCNQ1 cluster on human chromosome 11p15.5 and has been found to be strongly correlated with the development of cancer [12]. Nakano [13] et al. observed the high expression of KCNQ1OT1 transcription in CRC tissues and cell lines. What’s more, the research of Qi et al. [14] demonstrated that the KCNQ1OT1 knockdown sensitized osteosarcoma cells to cisplatin-induced apoptosis. Ren et al. [15] found that KCNQ1OT1 promoted chemoresistance of lung adenocarcinoma cells. These data hinted that KCNQ1OT1 may play a role in the cisplatin resistance in cancer. Moreover, increasing evidence confirmed that LncRNAs could function as competing endogenous RNAs (ceRNAs), binding to miRNA and removing the suppressive effect of them on mRNA expression [16]. Using a bioinformatics database (LncBase v.2), we found there were potential binding sites between KCNQ1OT1 and miR-497. Therefore, we wondered whether KCNQ1OT1 took part in the cisplatin resistance in CRC via removing the inhibitory effect of miR-497 on Bcl-2.

Curcumin is a natural phenolic compound extracted from Curcuma longa, which exhibits a strong anti-tumor effect [17]. Over the years, several researchers revealed the potential effect of curcumin to fight against cisplatin-resistant cancer cells while the specific mechanism remains unclear [18]. A recent study showed that curcumin suppressed cisplatin resistance in ovarian cancer via restoring LncRNA MEG3 expression [19], suggesting that curcumin may modulate cisplatin resistance in cancer cells via regulating LncRNAs.

Based on the previous studies, the present study set out to explore the role of KCNQ1OT1 in cisplatin-resistant CRC cells and whether KCNQ1OT1 participated in the reversal effect of curcumin on cisplatin resistance in CRC.

Materials and methods

Cell culture and transfection

Human CRC cell line HCT8 and cisplatin-resistant CRC cell line HCT8/DDP were purchased from Oulu Biotechnology (CHN) and maintained in RPMI-1640 medium (GIBCO, USA) containing 10% fetal calf serum (GIBCO) supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin (all purchased from Sigma, USA).

RNAi vectors (si-KCNQ1OT1 and miR-497 inhibitor), overexpression vectors (KCNQ1OT1 vector and miR-497 mimic), and relative negative controls (si-NC, inhibitor NC, vector, and mimic NC) were produced by RIBOBIO (CHN). For transfection, HCT8/DDP cells were seeded in 6-well plates with a concentration of 4 × 10^5 cells/well. Twenty-four hours later, 5 µg plasmid were transfected into HCT8/DDP cells utilizing Lipofectamine 3000 (Invitrogen, USA). Six hours later, the original medium was replaced with fresh RPMI-1640 complete medium. Forty-two hours later, the transfection efficiency was analyzed by qRT-PCR. The sequence of si-KCNQ1OT1 was 5′-GGUCAAAUAUGUCUUAAUA-3′ (Sense), 5′-UUUAGAACAUUUUGACCAGA-3′ (Antisense). si-NC was used as a negative control, 5′-AGCAGCGCCTTTGTAGGATTCC′-3′ (Sense), 5′-GCAATCCTACAAAGCGCGC-3′ (Antisense).

Quantitative real-time PCR (qRT-PCR)

Trizol reagent (Invitrogen, USA) was used to extract total RNA from 1 × 10^6 cells or 60 mg tumor tissues of mice. After reverse transcription, the qRT-PCR assay was conducted using the ABI 7500 Real-Time PCR System (Applied Biosystems, USA). β-actin or U6 was used as an endogenous control.

Western blot

The determination of protein levels of Bcl-2, Bcl-2 associated X (Bax), cleaved caspase 3, caspase 3, cleaved poly (ADP-ribose) polymerase 1 (PARP-1), and cytochrome C were done by western blot. The primary antibodies used in this study were as follows: anti-Bcl-2 antibody (1:2000; ab182858, Abcam, UK), anti-Bax antibody (1:5000; ab32503, Abcam), anti-cleaved caspase 3 antibody (1:500; ab32042, Abcam), anti-pro caspase 3 antibody (1:10,000; ab32499, Abcam), anti-cleaved PARP-1 antibody (1:5000; ab32064, Abcam), anti-cytochrome C antibody (1:5000; ab133504, Abcam), and anti-GAPDH antibody (1:2500; ab9485, Abcam).
Cell proliferation assay

Cell Counting Kit-8 (CCK-8) purchased from CoWin Biosciences (CHN) was used to determine cell proliferation. After indicated transfection, HCT8/DDP cells were seeded in 96-well plates with a concentration of $2 \times 10^3$ cells/well and cultured in 100 µL RPMI-1640 medium with or without curcumin (10 µM). After incubation for 0, 24, 48, 72, 96 h, 10 µl CCK-8 was added into each well and cells were cultured at 37°C for 2 h. Utilizing a microplate reader (Bio-Rad, USA), the optical density (OD) value of each well was detected at 450 nm.

Cell apoptosis analysis

Cell apoptosis was evaluated by flow cytometry using Annexin V-FITC Apoptosis Detection Kit (Univ-bio, CHN). Briefly, HCT8/DDP cells were resuspended in binding buffer at a concentration of $1 \times 10^6$ cells/mL. Then, 5 µl Annexin V-FITC was added into 50 µl cell suspension in the dark. Fifteen minutes later, the complex was reacted with 5 µl propidium iodide staining solution (PI) for 15 min. Cell apoptosis was measured by the CytoFLEX flow cytometer (Beckman Coulter).

Dual-luciferase reporter gene assay

The binding sites between KCNQ1OT1 and miR-497 were predicted by LncBase v.2 and the binding sites between miR-497 and Bcl-2 were predicted by Miranda. Twenty-four hours before the assay, HCT8/DDP cells were seeded in 24-well plates with a concentration of $2 \times 10^5$ cells/well. To confirm the combination of KCNQ1OT1 and miR-497, the HCT8/DDP cells were cotransfected with KCNQ1OT1 wild type (WT) luciferase reporter/KCNQ1OT1 mutant type (MUT) luciferase reporter and miR-497 mimic/mimic NC. Forty-eight hours later after transfection, cells were collected and the luciferase activity was measured. The combination of miR-497 and Bcl-2 was confirmed using the same way.

RNA pull-down assay

RNA pull-down assay was performed as previously described [20]. KCNQ1OT1 was combined with biotin utilizing the Biotin RNA Labeling Mix purchased from Roche (CH). Bio-probe NC was used as a negative control. The Bio-KCNQ1OT1 probe and Bio-probe NC were, respectively, incubated with whole-cell lysates from $1.5 \times 10^7$ HCT8/DDP cells, followed by the incubation of streptavidin agarose magnetic beads. One hour later, miR-497 level in the complex pulled down by the Bio-KCNQ1OT1 probe and Bio-probe NC was detected by qRT-PCR.

Xenograft animal experiments

Male six-week-old nude mice ($n = 24$) were purchased from SLAC Laboratory Animal Co., Ltd (CHN). The lentivirus-KCNQ1OT1 (lenti-KCNQ1OT1) and negative control (lenti-NC) were provided by RIBOBIO (CHN). Mice were divided into 4 groups: vehicle (10% dimethyl sulfoxide; $n = 6$), curcumin ($n = 6$), curcumin + lenti-NC ($n = 6$), curcumin + lenti-KCNQ1OT1 ($n = 6$). In the vehicle or curcumin group, $1 \times 10^6$ HCT8/DDP cells were subcutaneously injected into the back of mice. Once the tumor size reached 100 mm³, mice were randomly intraperitoneally injected with curcumin (1 g/kg/week) or equal vehicle. In curcumin + lenti-NC or curcumin + lenti-KCNQ1OT1 groups, $1 \times 10^6$ HCT8/DDP cells transfected with lenti-KCNQ1OT1 or lenti-NC were suspended in Matrigel matrix (BD Biosciences, USA) and subcutaneously injected into the back of mice. Once the tumor size reached 100 mm³, the mice intraperitoneally injected with vehicle or curcumin (1 g/kg/week). The tumor volume of each mouse was measured every seven-day from day 7 to day 42 after tumor cell implantation. Then, the mice were sacrificed and the tumor tissues were collected. All experiments were performed in accordance with the 2009 draft of the Animal Protection Law of the People’s Republic of China pertaining and approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (ethical project number: YS2019-275).

Statistical analysis

Data were shown as mean ± SD. Statistical analysis was performed using GraphPad Prism 6.0. Data were analyzed by student’s t-test (for two experimental groups) or one-way ANOVA (for multiple experimental groups). Results were considered statistically significant when $P < 0.05$.

Results

KCNQ1OT1 was up-regulated in HCT8/DDP cells

As depicted in Fig. 1a and b, compared with HCT8 cells, the HCT8/DDP cells displayed higher KCNQ1OT1 expression and lower miR-497 expression. In addition, apparent increases in Bcl-2 mRNA and Bcl-2/Bax ratio were observed in HCT8/DDP cells (Fig. 1c, d). Meanwhile, the protein levels of cleaved caspase 3, a pro-apoptosis protein [21], cleaved PARP-1, a
marker of cells undergoing apoptosis [22], and cytochrome C were downregulated in HCT8/DDP cells (Fig. 1d, e).

**KCNQ1OT1 functioned as a regulator of HCT8/DDP cells’ proliferation and apoptosis**

To investigate the functions of KCNQ1OT1 on the proliferation and apoptosis of cisplatin-resistant CRC cells, si-KCNQ1OT1#1, #2, #3 and si-NC were transfected into HCT8/DDP cells. As shown in Fig. 2a, the qRT-PCR analysis confirmed that si-KCNQ1OT1#2 exhibited the best inhibition efficiency on KCNQ1OT1 expression. Thus, we selected si-KCNQ1OT1#2 (hereafter written as si-KCNQ1OT1) to interfere KCNQ1OT1 expression in further study. The viability of si-KCNQ1OT1-transfected HCT8/DDP cells was markedly decreased compared with those cells transfected with si-NC (Fig. 2b). Flow cytometry assay demonstrated that si-KCNQ1OT1 transfection resulted in a significant elevation of the apoptotic HCT8/DDP cells (Fig. 2c, d).

**KCNQ1OT1 released Bcl-2 expression via sponging miR-497**

Using bioinformatics software (LncBase v.2), we found there were several potential binding sites between KCNQ1OT1 and miR-497 (Fig. 3b). To confirm the endogenous combination between KCNQ1OT1 and miR-497 in HCT8/DDP cells, RNA pull-down assay and dual-luciferase reporter assay were performed. As depicted in Fig. 3a, compared with Bio-probe NC, a great quantity of miR-497 was detected in the complex pulled down by the Bio-KCNQ1OT1 probe. Meanwhile, miR-497 mimic, rather than mimic NC, markedly decreased the luciferase activity of KCNQ1OT1 WT (Fig. 3c). What’s more, the miR-497 expression level was suppressed by KCNQ1OT1 overexpression (Fig. 3f) and promoted by KCNQ1OT1 knockdown (Fig. 3h). These data verified the interaction between KCNQ1OT1 and miR-497 in HCT8/DDP cells. Zhu et al. [23] revealed the combination of miR-497 and Bcl-2 in human glioma cells. To determine
whether miR-497 could also target Bcl-2 in HCT8/DDP cells, the following experiments were conducted. As shown in Fig. 3d and e, the luciferase activity of Bcl-2 3′ UTR WT was significantly suppressed in the presence of miR-497 mimic. Besides, the miR-497 overexpression suppressed the Bcl-2 protein level (Fig. 3g) and miR-497 knockdown elevated the Bcl-2 protein level (Fig. 3i). The negative regulation of miR-497 on the Bcl-2 protein level was eliminated by KCNQ1OT1 (Fig. 3g, i), demonstrating that KCNQ1OT1 functioned as a sponge of miR-497 and removed its regulatory effect on Bcl-2. What’s more, the regulatory effect of miR-497 on the cleaved PARP-1 protein level and Bcl-2/Bax ratio was abrogated by KCNQ1OT1 (Fig. 3g, i), hinting that KCNQ1OT1 suppressed cell apoptosis via inhibiting miR-497 expression.

**KCNQ1OT1 mediated the regulatory effect of curcumin on proliferation and apoptosis of HCT8/DDP cells**

We next sought to determine whether KCNQ1OT1 was involved in the suppressive effect of curcumin on cisplatin resistance in CRC cells. First, as shown in Fig. 4a and b, curcumin supplementation appreciably inhibited cell proliferation and KCNQ1OT1 expression in a dose-dependent manner. Considering curcumin exhibited the best inhibition effect at a concentration of 10 µM, we selected this concentration in the next experiments. Second, KCNQ1OT1 was overexpressed in HCT8/DDP cells by transfecting the KCNQ1OT1 vector (Fig. 4c). The curcumin + KCNQ1OT1 vector-treated HCT8/DDP cells had a much higher Bcl-2/Bax ratio and lower protein levels of cytochrome C, cleaved caspase 3, and cleaved PARP-1 than that of the curcumin + vector-treated cells (Fig. 4d). What’s more, the curcumin treatment effectively repressed cell proliferation and boosted the apoptotic cell numbers, while the overexpression of KCNQ1OT1 reversed the effect of curcumin on HCT8/DDP cells, manifesting as elevating cell proliferation and suppressing cell apoptosis in curcumin-treated HCT8/DDP cells (Fig. 4e–g).

**KCNQ1OT1 mediated the regulatory effect of curcumin on proliferation and apoptosis of HCT8/DDP cells through miR-497**

To further explore whether KCNQ1OT1 took part in the suppressive effect of curcumin on cisplatin resistance in CRC
we over-expressed miR-497 in curcumin-treated HCT8/DDP cells in the presence of KCNQ1OT1 vector (Fig. 5a). Importantly, the miR-497 overexpression abrogated the KCNQ1OT1 overexpression-induced up-regulation of Bcl-2 expression (Fig. 5b) and cell viability (Fig. 5c). Also, in response to the transfection of miR-497 mimic, the cell apoptosis retarded...
by KCNQ1OT1 overexpression was elevated again (Fig. 5b, d, e).

**KCNQ1OT1 reversed the suppressive effect of curcumin on the growth of cisplatin-resistant CRC cells in vivo**

To confirm whether KCNQ1OT1 could mediate the regulatory effect of curcumin on cisplatin-resistant CRC cells in vivo, a mouse xenograft model was established and KCNQ1OT1 was ectopically overexpressed using lenti-KCNQ1OT1 in curcumin-treated xenograft model mice (Fig. 6c). As shown in Fig. 6a and b, compared with vehicle, the curcumin decreased the levels of tumor volume (Fig. 6a) and tumor weight (Fig. 6b) in xenograft model mice. What’s more, be similar to the results of in vitro experiments, the curcumin treatment decreased KCNQ1OT1 expression (Fig. 6c), and Bcl-2 protein level (Fig. 6e), while elevated miR-497 expression and the protein levels of cleaved PARP-1 and Bax (Fig. 6d, e). On the contrary, the KCNQ1OT1 overexpression removed the
promoting effect of curcumin on miR-194 expression and the protein levels of cleaved PARP-1 and Bax (Fig. 6d, e). Meanwhile, the KCNQ1OT1 overexpression removed the suppressive effect of curcumin on Bcl-2 protein (Fig. 6e).

**Discussion**

Cisplatin is widely used for chemotherapy of CRC [24]. Nevertheless, chronic cisplatin exposure of CRC cells give rise to the cisplatin resistance, ultimately resulted in the chemotherapy failure [25]. Herein, in this study, we demonstrate that KCNQ1OT1 promoted proliferation and inhibited apoptosis of cisplatin-resistant CRC cells via the miR-497/Bcl-2 axis. Meanwhile, the reversal effect of curcumin on cisplatin resistance in CRC cells was dependent on its negative regulation of KCNQ1OT1 expression.

KCNQ1OT1 has been reported to be a promoter of cancer progression via regulating cancer cell proliferation, invasion, and apoptosis. For instance, Wang et al. [26], reported that KCNQ1OT1 aggravated cell proliferation and migration in bladder cancer via sponging miR-145-5p. Kang et al. [27]...
found that KCNQ1OT1 contributed to the progression of non-small cell lung cancer by releasing autophagy-related gene 3 expressions. All of these findings manifested the importance of KCNQ1OT1 in the development of cancer.

Recently, the role of KCNQ1OT1 in cisplatin resistance of cancer cells aroused wide interest among researchers. Zhang et al. [28] revealed that KCNQ1OT1 could aggravate cisplatin resistance in tongue cancer via acting as a ceRNA of miR-211-5p. In our present study, we found that compared with normal CRC cell line HCT8, the cisplatin-resistant CRC cell line HCT8/DDP exhibited a higher expression level of KCNQ1OT1 (Fig. 1). In addition, KCNQ1OT1 overexpression suppressed apoptosis of cisplatin-resistant CRC cells in vitro (Fig. 2) and accelerate tumorigenesis in vivo (Fig. 6). Interestingly, the research of Li et al. [29] demonstrated that KCNQ1OT1 enhanced oxaliplatin resistance in CRC via inducing protective autophagy. Combined our experimental results with previous studies, KCNQ1OT1 could function as a positive regulator in chemoresistance of various cancers, including CRC.

Increasing evidence supported that apoptosis failure is a crucial reason for the development of chemotherapy resistance [30]. As a key anti-apoptotic protein, Bcl-2 is involved in the multidrug resistance of CRC cells [31]. In line with the previous study, an apparent elevation of the Bcl-2 protein level was observed in HCT8/DDP cells (Fig. 1). Besides, the subsequent study showed that Bcl-2 was the target of miR-497 while KCNQ1OT1 released Bcl-2 expression via sponging miR-497 (Fig. 3). miR-497 is a well-known anti-oncogene and the auxo-action of the miR-497/Bcl-2 axis on chemotherapy sensitivity has been reported in myeloma [32]. In the present study, miR-497 overexpression abrogated the promoting effect of KCNQ1OT1 on cell viability and the inhibitory effect of KCNQ1OT1 on cell apoptosis in HCT8/
DDP cells via inhibiting Bcl-2 expression (Fig. 5), proving that miR-497/Bcl-2 axis could also suppress cisplatin resistance in CRC cells.

Curcumin is a natural phenolic compound and has the advantages of small adverse reactions, good safety, and low price [33]. Numerous studies clarified that curcumin had the property of reversing chemotherapy drug resistance of tumors [34]. For example, in CRC, curcumin reversed oxaliplatin resistance via regulating the process of epithelial-mesenchymal transition [35]. What’s more, Liu et al. [36] reported that the regulatory effect of curcumin on LncRNAs in CRC. Therefore, we speculated that curcumin may reserve chemotherapy drug resistance in CRC via modulating LncRNAs. As we speculated, in the present study, curcumin dose-dependently decreased the viability of HCT8/DDP cells and the expression of KCNQ1OT1 (Fig. 4). KCNQ1OT1 overexpression abrogated the reversal effect of curcumin on cisplatin-resistant in vitro (Fig. 4) and removed the inhibitory effect of curcumin on tumorigenesis in vivo (Figs. 6), proving that curcumin suppressed cisplatin resistance via downregulating KCNQ1OT1.

In summary, we reported that KCNQ1OT1 promoted cisplatin resistance in CRC cells and the administration of curcumin could reserve the cisplatin resistance in CRC cells through down-regulating KCNQ1OT1 expression. We hope that our findings could provide new intervention targets for the prevention and reversal of cisplatin resistance during CRC therapy.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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