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Salidroside suppresses the activation of nasopharyngeal carcinoma cells via targeting miR-4262/GRP78 axis

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ABSTRACT

To study the effect of Salidroside on nasopharyngeal carcinoma (NPC) cells and its mechanism. NPC cells were cultured, MTT was used to detect the effect of Salidroside on cell proliferation, apoptosis detected by flow cytometry assay, Western blot was used to detect the related protein expression. MiR-4262 and GRP78 used qRT-PCR for evaluation. Mimics/mimic NC and miR-4262 inhibitor/inhibitor NC were transfected into CNE2 and HONE1 cell lines, and cell viability was detected by MTT. Caspase-3, −8 and −9 activities were detected by caspase colorimetric assay kit. Targetscan predicted that downstream target of miR-4262. Relative luciferase activity was detected by luciferase assay. The effect of Salidroside on the growth of transplanted tumor in nude mice was observed. After Salidroside treatment, cell proliferation decreased and apoptosis increased, Bax protein expression increased and Bcl-2 decreased; miR-4262 expression level in nasopharyngeal carcinoma tissues was lower than that in adjacent tissues. GRP78 was the target of miR-4262 and downregulate the expression of miR-4262 in NPC cells can increase the expression of GRP78, and the expression of GRP78 decreased after upregulating the expression of miR-4262. Salidroside could inhibit the growth of NPC xenografts in nude mice. The level of Bax was increased and Bcl-2 was decreased in Salidroside group. Salidroside can significantly inhibit the proliferation and promote the apoptosis of NPC cells via regulating miR-4262/GRP78 signal axis.

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Introduction

NPC is a malignant tumor occurring on the top and side walls of the nasopharynx. It is one of the most frequent malignant tumors in China. The incidence rate is the first of the otorhinolaryngology malignant tumors. Approximately, 75%–90% of NPC patients are locally advanced and have cervical lymph node metastasis at the time of initial diagnosis [1,2]. Although the local control rate of NPC has been significantly improved by the combination of radiotherapy and chemotherapy, there is still no early prediction and effective intervention for NPC distant metastasis and the metastasis rate as well as survival rate has not improved significantly. Once recurrence or metastasis, the prognosis is poor [3–5]. Most of NPC is moderately sensitive to radiotherapy, and it is the preferred treatment for NPC [6]. At present, surgical resection and chemotherapy are also indispensable treatment method for patients with well-differentiated NPC, later period of disease and recurrence after radiotherapy [7]. But the side effects of radiotherapy and chemotherapy for NPC are also great. Therefore, it is the key to actively seek effective and safe new treatment approaches and drugs to effectively control the metastasis of NPC and improve the survival rate of patients

Salidroside is the extract of rhodiola root, molecular formula: c14h20o7, molecular weight: 300.3044, the effective component is Salidroside, which with sweet and bitter taste [8]. Studies have shown that rhodiola has the effects of enhancing immune function, protecting cardiovascular, resisting cancer and depression [9,10]. Therefore, Salidroside shows the potential as an anticancer drug. The previous studies in mice showed that Salidroside can directly inhibit the growth and metastasis of transplanted lung cancer, and the combination of Salidroside and anti-tumor drug

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cyclophosphamide in the treatment of breast cancer and lung cancer effectively improves the antitumor and anti-metastasis efficacy [11,12]. However, there is no report about Salidroside in NPC. Therefore, this study explored the efficacy and mechanism of Salidroside in the treatment of NPC in vivo and in vitro.

MicroRNAs (miRNAs) play an important role in tumorigenesis and development [13]. Studies have found that miR-4262 is involved in the malignant biological behavior of tumor [14], but its regulatory mechanism is unclear and has not been reported yet. Therefore, this study also clarified the molecular mechanism of miR-4262 regulating the malignant biological behavior of NPC.

Methods

Patients and tissue samples

According to the ethics committee of the participating agencies and the Helsinki declaration, patient samples were obtained with written informed consent. This study was approved by the institutional review committee of Jinan central hospital. Tissue samples were collected from 30 NCP patients (aged 18–80 years) who underwent surgical resection in Jinan Central Hospital from 2018 to 2020. All patients were diagnosed by histopathology according to the clinical protocol, and none of them received preoperative chemotherapy or immunotherapy. All staining sections were independently evaluated and scored by two pathologists, and the clinicopathological results of the patients were not known in advance.

Cell culture and transfection

The human nasopharyngeal carcinoma cell lines (CNE2 and HONE1) were brought from the ATCC company (ATCC, USA). These cells were grown in RPMI-1640 medium (Gibco, USA) containing 10% fetal bovine serum (FBS, Gibco, USA). All cells were grown at room temperature in a humidified atmosphere with 5% CO_2. The mimics control, miR-4262 mimics, inhibitor control as well as miR-4262 inhibitor were brought from RiboBio company (RiboBio, Guangzhou, Chinese). Cells were incubated in 6-well plates and transfected with indicated constructs with Lipofectamine 3000 reagent (Invitrogen, USA).

MTT assay

The cell proliferation capability was determined with the MTT assay. In brief, cells were treated with Salidroside (0, 5, 20, 40 μM) for 24 h. Then the cell was harvested and placed into 96-well plates at density 1×10^4 cells/well. Subsequently, the cells were incubated for 48 h. Lastly, 5 mg/mL MTT solution (Beyotime, Shanghai, China) was placed to each well and incubation at room temperature for 2 h. We use a microplate reader (BioRad Laboratories, USA) to detect the absorbance at 490 nm wavelength.

Flow cytometry analysis

The cells were treated with Salidroside (Invivochem, USA; 0, 5, 20, 40 μM) for 24 h. Then the cell apoptosis ability was calculated through utilizing the annexin V-FITC/PI Apoptosis Detection Reagent (Thermo Fisher Scientific, USA) in accordance with supplier's protocol. Subsequently, the apoptotic cells were determined by utilizing a Beckman Coulter FACS flow cytometer (Beckman Coulter, USA) and assessed by FlowJo software system (Ashland, USA).

Caspase-3,8,9 activity detection

After 24 h of culture, the cells were suspended in 50 μL cold cell lysis buffer and stand still for 10 min. After centrifugation, the supernatant was transferred to another centrifuge tube and placed in ice. The mixture of reaction buffer/DTT and the substrate of capases-3, −8, −9 was added to each group. The OD value was read at 405 nm in water bath, and the activity unit of capases-3, −8, −9 was calculated.

Dual-luciferase reporter assay

Luciferase reporter vectors, GRP78 wild-type (GRP78-WT) or mutant (GRP78-Mut), insert with pGL3-basic plasmid (Promega, USA) were co-transfected with mimics control or miR-4262 mimics by using the Lipofectamine 3000 regents

(Invitrogen, USA). And the transfected cells were harvested after transfection for 72 h. We use the Luciferase reporter assay System to calculate the luciferase activities (Promega, USA). Each experiment was carried out in triplicates.

Quantitative real-time PCR assay

Total RNA from the human nasopharyngeal carcinoma cell lines (CNE2 and HONE1) was collected with Trizol reagent (Invitrogen, USA). The reverse transcription was carried out through using a Reverse Transcription kit (Thermo Fisher Scientific, USA). Subsequently, the cDNA was performed to PCR in a Thermal Cycler Dice Real-Time system (Takara, Japanese) with SYBR Green PCR master mix (Takara, Japanese). Experiment was carried out in triplicate and the relative of gene expression was measured with $2^{-\Delta\Delta Ct}$ method. Activate the polymerase with the following primers:

MiR-4262
Forward: 5′-TGCGGGACATTCAGA-3′,
Reverse: 5′-GGAGTGCAGGGTCCGAGGT-3′.
U6, snRNA (miR-4262 internal reference)
Forward: 5 ‘-CTCGCTTCGGCAGCACA-3′,
Reverse: 5′-AACGCTCACGAAYYYGCGT-3′.
GRP78
Forward: 5′-GATCCTACTGGACGGTTCGC-3′,
Reverse: 5′-CAGACACGGTTGCAGTTGAC-3′.
GAPDH, snRNA (GRP78 internal reference)
Forward: 5′-GGTCGGAGTCAACGGATTTG-3′,
Reverse: 5′-GGAAGATGGTGATGGGATTTC-3′.

Western blot analysis

The human nasopharyngeal carcinoma cell protein extraction was carried out following a previous study [15]. In short, the protein from bladder carcinoma cell lines was collected with RIPA lysis buffer (Sigma-Aldrich, USA) added with protease inhibitor cocktail (PIC, Roche, USA). Proteins were detached with 12% SDS-PAGE gel and transferred to PVDF membrane (Millipore, USA). Then, the membranes were blocked with 5% BSA at 37°C for 2 h. After wash with PBS, the membranes were incubation with primary antibody against GRP78 (1:2000, CST, USA), Bcl-2 (1:2000, CST, USA), Bax (1:1000, Abcam, USA) and GAPDH (1:2000, Proteintech, USA) at 4°C for 24 h. Next, the membrane was incubated with secondary antibody (1:10,000, Jackson, USA) at 37°C for 2 h. Blots were detected with ECL reagents (Amersham, UK) and assessed with ImageJ software (National Institutes of Health, USA).

Xenograft tumor model

The nude mice were bought from Shanghai SLAC Laboratory Animal company (Shanghai, China). Our animal research was authorized by the Ethics Review Committee of Jinan central hospital. The human nasopharyngeal carcinoma cells (1×10^6/mice) were treated with PBS or Salidroside (Invivochem, USA) and injected subcutaneously into the mice. The tumor volume was calculated weekly. The mice were sacrificed, and the tumor tissue was weighed after 35 days later.

Statistical analysis

All the experimental data were analyzed by SPSS19.0 statistical software (IBM Corp.) and GraphPad Prism 7.0 software (GraphPad Software, Inc.). The data analysis was presented as mean ± SD. Data analysis between the two groups was assessed through using Student’s t-test. Data analysis between multiple groups was assessed using the ANOVA method. A value of $P < 0.05$ was thought to be a statistically significant difference.

Result

1. Effects of salidroside on proliferation and apoptosis of CNE2 and HONE1 cells

Salidroside inhibited cell proliferation in a concentration-dependent manner (Figure 1(a)). Flow cytometry (annexin V/PI double staining) confirmed that Salidroside promoted apoptosis of CNE2 and HONE1 cells in a concentration-

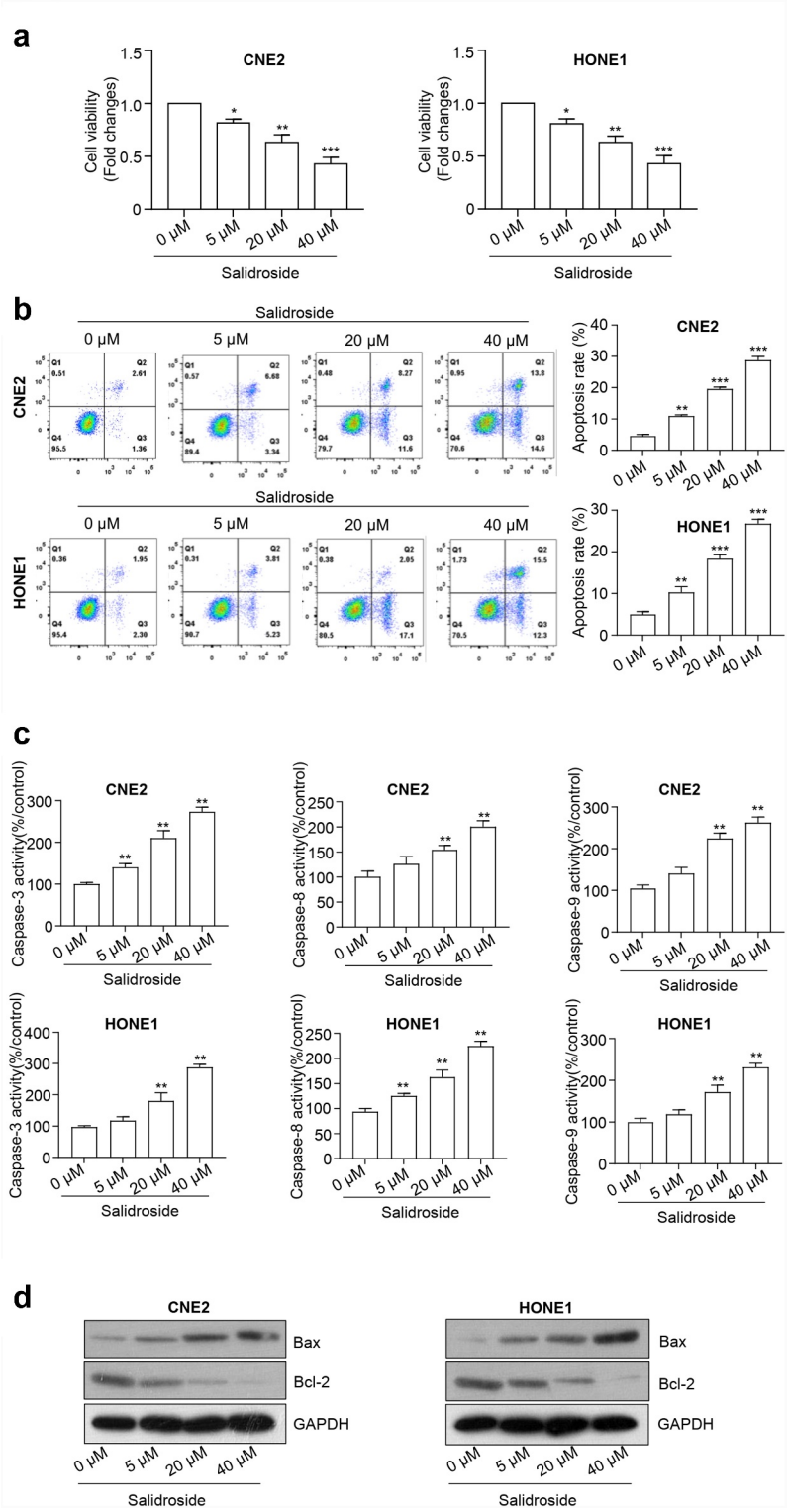

Figure 1. Salidroside inhibits viability and promotes apoptosis in CNE2 and HONE1 cell lines.

A. MTT was used to detect the effect of salidroside on cell proliferation in CNE2 and HONE1 cell lines. The results showed that Salidroside inhibited cell proliferation in a concentration dependent manner.**B**. Flow cytometry assay was used to evaluate the apoptosis of CNE2 and HONE1 cell lines which were treated with Salidroside and confirmed that Salidroside promoted apoptosis of cells in a concentration dependent manner.**C**. Increased caspase-3, – 8 and – 9 activities were detected by caspase colorimetric assay kit to confirm the role of Salidroside.**D**. Representative Western blots of the protein expression levels for cell proliferation and apoptotic biomarkers in CNE2 and HONE1 cell lines treated with different concentration Salidroside, GAPDH was used as an internal reference. The result showed that Salidroside can promote the expression of Bax and inhibited Bcl-2 in a concentration dependent manner. *$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$.

dependent manner (Figure 1(b)). The activities of Caspase-3, −8 and −9 increased in CNE2 and HONE1 cells after treatment with different concentration Salidroside for 48 h (Figure 1c). The results of Figure 1(d) showed that Salidroside can promote the expression of Bax and inhibited Bcl-2 in a concentration-dependent manner (Figure 1(d)).

2 Salidroside can upregulate miR-4262 expression in NPC

MiRNA microarray results showed that Salidroside induced up regulation of miR-4262 expression (Figure 2(a)). The results of qRT-PCR confirmed Salidroside caused the increase of miR-4262 in CNE2 and HONE1 cells, and the expression level of miR-4262 in NPC tissues was lower than that in adjacent tissues (Figure 2(b)). As shown in Figure 2(c), compared with miR-NC co-transfection control, co-transfection Salidroside could significantly decrease CNE2 and HONE1 cell viability, but this phenomenon disappeared when Salidroside co-transfection miR-4262 inhibitor, confirmed that Salidroside can upregulate miR-4262 expression (Figure 2(c)). The corresponding protein expressions of BAX and Bcl-2 also verified this conclusion (Figure 2(d)).

3 MiR-4262 inhibits the expression of GRP78 by binding with 3′UTR of GRP78

Targetscan predicted that GRP78 is a target of miR-4262 (Figure 3(a)). Luciferase reporter assay confirmed that the overexpression of miR-4262 inhibited the luciferase activity of wide-type (WT) GRP78, while mutation (Mut) of this binding motif rescued the inhibitory effect (Figure 3(b)). In CNE2 and HONE1 cell lines, the qRT-PCR and western bolt revealed that compared with NC group, miR-4262 mimics significantly decreased GRP78 protein and mRNA expression, and miR-4262 inhibitor significantly increased GRP78 protein and mRNA expression (Figure 3(c, d)). All the experimental results proved that miR-4262 can negatively regulate GRP78.

4 Salidroside suppresses the tumor growth by miR-4262/GRP78 signial pathway

As shown in Figure 4(a), the tumor volume and weight in nude mice treated with Salidroside were significantly lower than those in the control group (Figure 4(a)). The results of qRT-PCR showed that Salidroside increased the expression of miR-4262 (Figure 4(b)) and the Western blot results showed that Bax increased but Bcl-2 decreased in Salidroside group (Figure 4(c)).

Discussion

NPC is the most common head and neck malignant tumor in southern China [16]. The incidence rate of population standardization in the world is as high as 30/10 million, and frequently found in young adults [1]. The incidence rate of NPC is significantly higher than that of 30 years old and reaching a peak at 50 – 59 years old [2]. NPC is a kind of tumor that is sensitive to chemoradiotherapy. Studies have shown that in the systemic treatment of distant metastasis of NPC, the effective response rate of standard first-line treatment (platinum containing dual-chemotherapy regimen) is 70–80%. However, the effective response rate of second-line treatment (such as docetaxel monotherapy regimen) is only 30–40% when platinum drug resistance [17,18]. In addition, studies have also shown that 5–15% of patients with intensity-modulated radiation therapy (IMRT) will have local recurrence after treatment, and 15–30% of patients will have distant recurrence after treatment. As the only alternative treatment for most patients with recurrence and metastasis, chemotherapy has reached the upper limit. The median survival time of patients with recurrent and metastatic NPC after chemotherapy is up to 10 months. Only a few young patients with single metastasis can obtain a survival time of more than 5 years [19,20]. Our study investigated the anti-cancer activity of Salidroside in NPC cells through repressing cell proliferation and apoptosis. In addition, we first found this function was associated with miR-4262/GRP78 signaling pathway.

Salidroside is one of the important components in the traditional Chinese medicine rhodiola. As

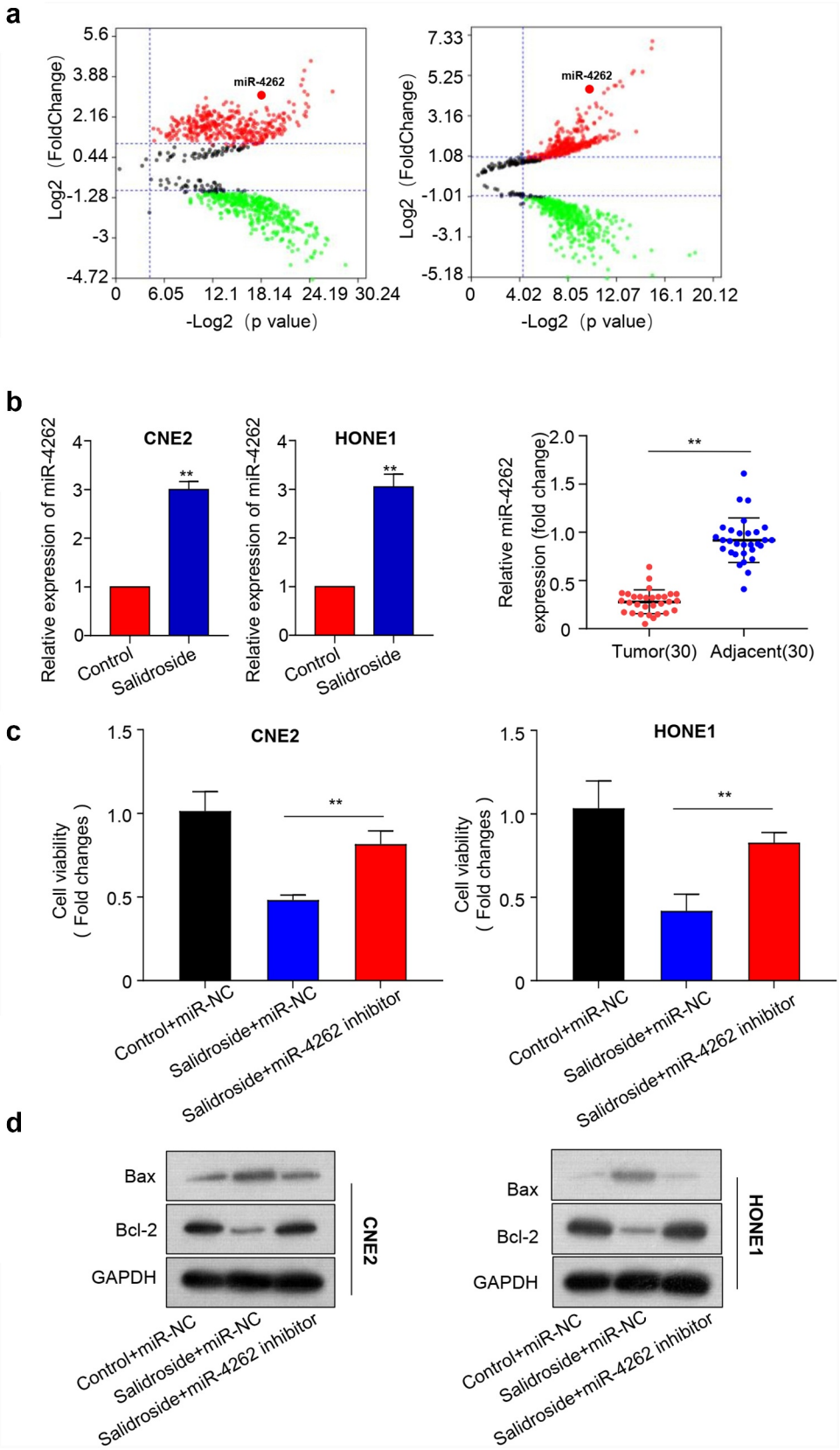

Figure 2. Salidroside can upregulate miR-4262 expression to inhibit cell viability in CNE2 and HONE1 cell lines.

A. MiRNA microarray was used to determine the induced regulation of miR-4262 expression in CNE2 and HONE1 cell lines treated with Salidroside.**B**. QRT-PCR was used to detected the increased level of miR-4262 in CNE2 and HONE1 cell lines treated with Salidroside, and the low-expression in 30 pairs of NPC patients' tumor and adjacent cells.**C**. Relative cell viability of CNE2 and HONE1

cells with Salidroside or miR-4262 inhibitor-treated were measured using MTT. The results showed that co-transfection Salidroside could significantly decrease CNE2 and HONE1 cells viability, but the effect disappeared when Salidroside co-transfection miR-4262 inhibitor.**D**. Relative protein expression levels of BAX and Bcl-2 in Salidroside or miR-4262 inhibitor-treated CNE2 and HONE1 cells were measured using Western blots. The results showed that co-transfection Salidroside could significantly decrease Bcl-2 level and BAX increased, but the effect disappeared when Salidroside co-transfection miR-4262 inhibitor. $^{**}p < 0.01$.

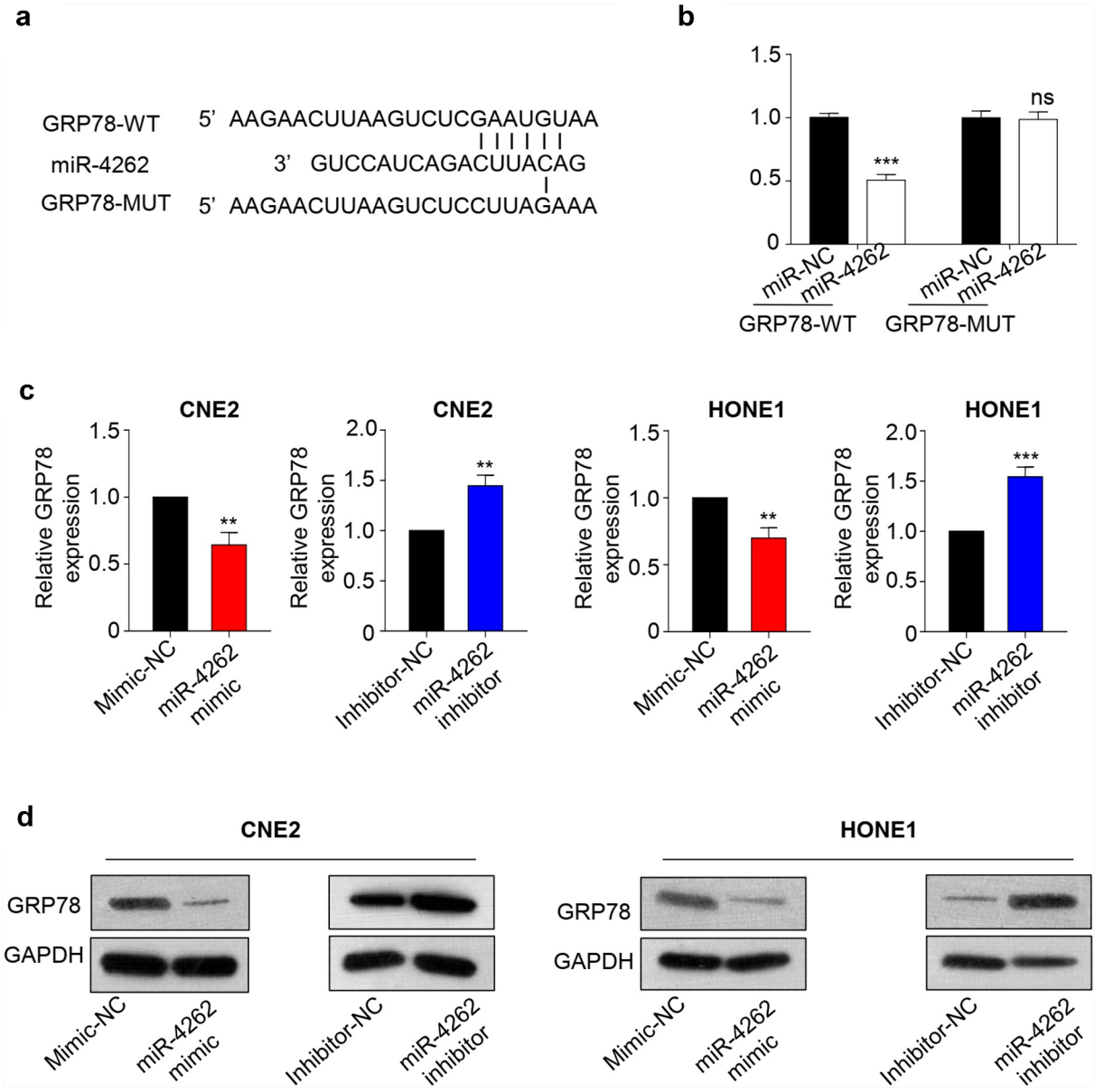

Figure 3. miR-4262 directly interacts with GRP78 and have a negative correlation.

A. A predicted binding site of miR-4262 within GRP78 using the Targetscan. And predicted that GRP78 is a target of miR-4262.**B**. Dual-luciferase reporter was used to determine the interaction between miR-4262 and GRP78. And confirmed that the over-expression of miR-4262 inhibited the luciferase activity of GRP78.**C**. Relative levels of GRP78 in miR-4262-overexpressed CNE2 and HONE1 cells were measured using qRT-PCR. The results showed that miR-4262 mimics significantly decreased GRP78 mRNA expression, and miR-4262 inhibitor significantly increased GRP78 mRNA expression**D**. Representative Western blots of CNE2 and HONE1 cells transiently transfected with miR-NC or miR-873-5p mimics. The results showed that miR-4262 mimics significantly decreased GRP78 protein expression, and miR-4262 inhibitor significantly increased GRP78 protein expression The data are normalized to GAPDH and presented as mean ± SD of two experiments. $^{**}p < 0.01$, $^{***}p < 0.0001$.

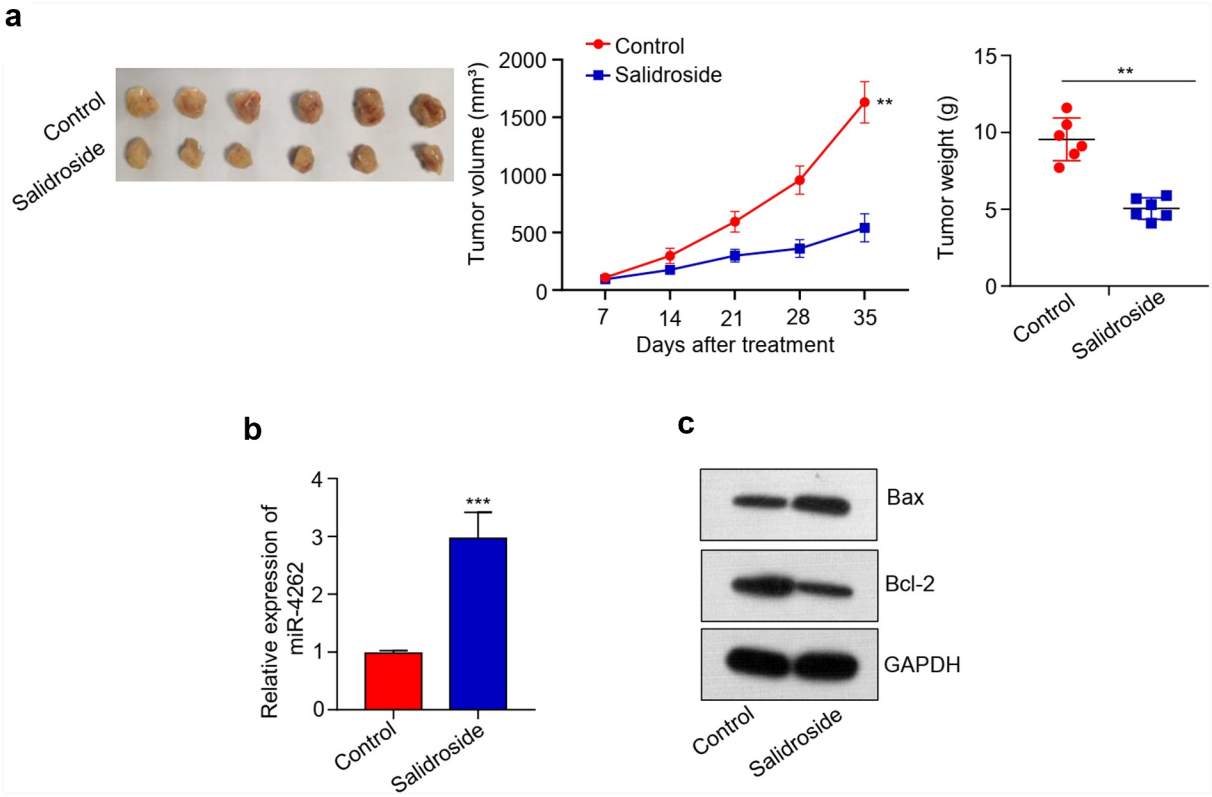

Figure 4. Salidroside suppresses the viability of NPC cells via targeting miR-4262/GRP78 axis.

A. The lower tumor volume and weight in the treatment group were measured to confirm the Salidroside efficacy in vivo.**B**. QRT-PCR was used to detect the increased miR-4262 expression in tumor treated with Salidroside.**C**. The increased expression levels of Bax and decreased expression levels of Bcl-2 were detected by Western blots. $^{**}p < 0.01$, $^{***}p < 0.0001$.

a traditional Chinese medicine rich in polysaccharides and immune active substances, Salidroside has been widely used in the prevention of altitude sickness, anti-aging, anti-depression, anti-tumor, and fatigue elimination [21]. Currently, accumulating evidence suggests Salidroside could exert a tumor-suppression effect on diverse malignant tumor progression. For instance, Li Hai et al. study reported that inhibition of autophagy could enhance synergistic effects of salidroside and antitumor agents against colorectal cancer [22]. Zhandong et al. study found that salidroside was able of improving the chemosensitivity of gastric cancer to Apa and the iVR1-NPs-Apa/Sal was capable of realizing highly efficient of tumor-targeting drug delivery [23]. Li Rong et al. study reported that Salidroside inhibited the growth of gastric cancer and induced apoptosis and protective autophagy through the PI3K/Akt/mTOR pathway [24]. Ding Shou-Yong et al. study also reported that Salidroside inhibits viability and induces apoptosis of HCC both in vitro and in vivo, and this effect is partially mediated by activation of ER stress [25]. However, the function of Salidroside in the development of NPC remains unclear. In our study, we found that Salidroside could inhibit the proliferation of CNE2 and HONE1 cells in a concentration-dependent manner. In addition, Salidroside could also promote the apoptosis of CNE2 and HONE1 cells, and regulate the expression of Bax and Bcl-2, indicating that Salidroside had anti-nasopharyngeal effect in vitro. Suggesting that Salidroside could exert a tumor-suppression effect on the NPC progression.

Large amounts of evidences indicated that miRNAs play an important regulatory role in the process of NPC [26–29]. Many studies have reported that miR-4262 is abnormally expressed in a variety of tumors and play an antitumor role [18,30]. For instance, Lu Ren et al. study reported that miR-4262 could serve as a sponge

of lncRNA-CRNDE involve in the progression of cervical cancer [31]. Song, K., et al., study found that the level of miR-4262 was significantly decreased in osteosarcoma specimens and there was a negative correlation between miR-4262 and osteopontin inhibition of osteopontin mediated cell invasion [32]. Liu Chunbo et al. study also reported that Abnormal increase of miR-4262 promotes cell proliferation and migration by targeting large tumor suppressor 1 in gliomas [33]. However, the effect of miR-4262 on NPC is rarely reported. In this study, our data suggested that the expression of miR-4262 in human NPC tissues was significantly down-regulated and overexpression of miR-4262 significantly decreased the cell viability. Indicating that miR-4262 is an antioncogene and plays an important role in regulating the biological behavior of NPC cells.

The glucose-regulated protein, GRP78 (also referred as BiP or heat shock protein family A member 5, HSPA5), is a stress-inducible molecular chaperone that is evolutionarily conserved from yeast to humans. It is also a member of the HSP70 family [34,35]. In its inactive state, GRP78 maintains endoplasmic reticulum (ER) stress sensors and ER-associated proapoptotic machineries by sustaining ER protein folding capacity to regulate the balance between cancer cell survival and apoptosis [36]. Revealing that GRP78 play an important role in the malignant tumor progression and tumorigenesis. In our study, GRP78 was confirmed to be the target gene of miR-4262 and upregulate miR-4262 significantly inhibited the expression of GRP78, while down-regulation of miR-4262 showed the opposite effect, indicating that miR-4262 has a negative regulatory effect on GRP78 expression. However, the function of GRP78 in the progression of NPC remains in need of further study. Furthermore, our study also found that Salidroside increased the expression of miR-4262 and inhibited the expression of GRP78 in a concentration-dependent manner. In vivo experiments also confirmed that Salidroside could inhibit the growth of NPC xenografts in nude mice, promoting the apoptosis of transplanted tumor cells.

Conclusion

Salidroside can inhibit the growth of NPC and promote its apoptosis in vitro and in vivo, and its regulatory mechanism may be achieved through miR-4262/GRP78 signal pathway axis. Therefore, Salidroside is expected to become an important drug in the treatment of NPC.

Disclosure statement

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