RETRACTED ARTICLE: Long noncoding RNA HAGLROS promotes the process of mantle cell lymphoma by regulating miR-100/ATG5 axis and involving in PI3K/AKT/mTOR signal

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ABSTRACT
This research planned to grab the expression and impact of lncRNA HAGLROS in the biology and progression of mantle cell lymphoma. HAGLROS level in mantle cell lymphoma cell lines was detected, followed by investigation of the influences of HAGLROS silencing on Mino cell biological performances. Afterwards, the express patterns of HAGLROS vs. miR-100, as well as miR-100 vs. ATG5, were investigated. Furthermore, whether HAGLROS could regulate the signals of PI3K/AKT/mTOR was analyzed. HAGLROS level was high in mantle cell lymphoma cell lines. Silencing of HAGLROS inhibited Mino cell viability, increased apoptosis and decreased autophagy by sponging miR-100. Moreover, miR-100 targeted ATG5 fixed. Furthermore, HAGLROS suppression resulted in inhibition on the briskness of PI3K/AKT/mTOR signals. Concurrently HAGLROS suppression and miR-100 inhibitor markedly changed the impacts of HAGLROS down-regulation alone on activating PI3K/AKT/mTOR signals, which could further change after co-transfection of si-HAGLROS + miR-100 inhibitor + siATG5. Our findings point out that expression of HAGLROS is increased in mantle cell lymphoma cells and may function as an oncogene in mantle cell lymphoma. HAGLROS may promote tumour development by regulating miR-100/ATG5/PI3K/AKT/mTOR axis.

Introduction
Lymphoma is a group of blood cancers that originates from lymphocytes, and can be divided into Hodgkin and non-Hodgkin types. Mantle cell lymphoma is an uncommon and invasive subtype of non-Hodgkin lymphoma with a poor prognosis [1,2]. The annual incidence of mantle cell lymphoma has increased to 1–2 per 100,000 recently [3]. Despite a well therapeutic response at the beginning, the recurrence and chemoresistance is still high for patients with mantle cell lymphoma [4]. Therefore, there is a substantial need to disclose the deeper molecular biology underlying mantle cell lymphoma and explore potential biomarkers for the diagnosis and treatment of this disease.

Long noncoding RNAs (lncRNAs), transcripts with longer than 200 nucleotides in length, have emerged as important regulators of disease processes including cancer [5]. Several lncRNAs have been shown to exhibit a potential role in lymphomagenesis [6,7]. Usually, lncRNAs will run their functions through complete regulatory correlations, such as by targeting genes, proteins, or miRNAs [5]. It has been discovered that various kinds of miRNAs were targeted and regulated by lncRNAs in the progress of many diseases [5,7–9]. In mantle cell lymphoma, lncRNAs, such as ROR1-AS1 [8], MALAT1 [9], and LINK-A [10] have been proved to be correlated with the process of tumour development. However, there is limited study about the key lncRNAs in mantle cell lymphoma.

lncRNA HAGLROS, 699 bp in length, is reported to be involved in the processes of various cancers, such as gastric cancer [11], colon cancer [12], and osteosarcoma [13]. Whether HAGLROS is involved in the development of lymphoma remains to be fully discovered. In this research, we determined the level of HAGLROS in mantle cell lymphoma cells. The biological performances including viability, apoptosis and autophagy affected by HAGLROS were all evaluated by different kinds of experimental methods. Afterwards, comprehensive regulatory principles were also grabbed.

Materials and methods

Cell lines and culture
Five kinds of mantle cell lymphoma cell lines of Z-138, Mino, REC-1, Jeko-1, and JVM2 were purchased from ATCC (USA). Normal B lymphocytes were isolated from peripheral blood of 16 healthy donors (10 males and 6 females, average 45.6 ± 11.8 years old) using CD19 magnetic beads, followed by detachment with DETACHaBEAD CD19 (Invitrogen, USA).
All cells were maintained in RPMI 1640 medium mixed with 10% FBS (Gibco, Grand Island, NY).

**Cell transfection test**

Short hairpin RNA against HAGLROS (sh-HAGLROS#1 and sh-HAGLROS#2), shRNA negative control (sh-NC), miR-100 mimic, mimic NC, miR-100 inhibitor, inhibitor NC, pcDNA3.1, pcDNA-ATG5, small interfering RNA against ATG5(si-ATG5), and si-NC were purchased from Sangon Biotech (Shanghai, China). Cell transfection was conducted by Lipofectamine 2000 (Sangon Biotech) following the recommended protocols by the manufacturer. The silenced sequence of HAGLROS was shown as: sh-HAGLROS#1, CCUAUUUACUGCCAGGAGUTT, sh-HAGLROS#2, GGCUAAGACUGCGUGUAATT.

**Quantitative PCR (qPCR) test**

We isolated the total RNA in cells using TRIzol Reagent (Sangon Biotech). SMA 400 UV-VIS (Merinter, Shanghai, China) was chosen for the detection of the concentration and purity of the isolated RNA. Reverse transcription for complementary DNA (cDNA) synthesis was carried out through the reverse transcription system kit (Invitrogen). Based on a real-time PCR System (CFX96, Bio-Rad, Hercules, CA, USA), qPCR assays for detecting HAGLROS and ATG5 were carried out by the standard SYBR Green PCR kit, and GAPDH expression was chosen as the internal control; qPCR assays for detecting miR-100 were carried out by the TaqMan miRNA assay, and the PCR results were normalized using U6. Finally, 2^(-ΔΔCt) method was chosen for the detection of gene expressions.

**Western blotting test**

Total protein in cells was isolated from using NP-40 lysis buffer (Sangon Biotech), followed by detecting the concentration of the protein samples using the Bradford Protein Assay Kit (Sangon Biotech). After being loaded on 10% SDS-PAGE, the protein bands were transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). PVDF membranes were then blocked by 5% non-fat milk for 1 h at room temperature, probed with primary antibodies (1:1000, Abcam, Cambridge, MA, USA) at 4°C overnight, and incubated with the corresponding secondary antibody (horseradish peroxidase (HRP)-conjugated, 1:5000; Abcam) for 1 h at 37°C. Afterwards, the protein blots were evaluated with enhanced chemiluminescence reagents (Pierce, Rockford, IL, USA). β-actin was chosen as the internal control.

**MTT test**

The cell viability was evaluated using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide (MTT) assay at various times following different transfection. After cell transfection, cells were seeded in a 96-well plate and then incubated with 50 μL of MTT (Sigma–Aldrich, St. Louis, USA) at 37°C for 4 h. Then, the formazan crystals that appeared in viable cells was dissolved by adding with 150 μL of dimethyl sulfoxide (Sigma–Aldrich) at room temperature for 15 min. Absorbance at 470 nm was measured with a spectrophotometer (Eppendorf, Germany).

**Flow cytometry test**

Flow cytometry was chosen for the evaluation of cell apoptosis. Briefly, cells were washed and re-suspended in the buffer at a concentration of 1 × 10^6 cells/mL. Following the instructions of Annexin V-FITC Apoptosis Detection Kit (Sangon Biotech), cells were subsequently stained with Annexin V-FITC and PI for 15 min at room temperature. Data were analyzed using BD FACS Diva software (V6.1.3, BD Biosciences, San Jose, CA, USA).

**Target prediction and luciferase reporter assay**

Based on the information of Targetscanhuman, ATG5 was chosen as the theoretical target of miR-100, followed by validation of their target relationship by luciferase reporter method. Briefly, the full-length coding sequence of ATG5 containing the binding sequence of miR-100 (wild type) was synthesized from Sangon Biotech (Shanghai, China), then cloned into the pGL3 vectors (Sangon Biotech) to produce the luciferase reporter vector pGL3-ATG5-wt. Meanwhile, a QuikChange Site-Directed Mutagenesis kit (TaKaRa) was used for mutating the potential miR-100 binding sites in ATG5 gene, which was also inserted into the pGL3 vector to form the luciferase report vector pGL3-ATG5-mt. HEK293 cells were co-transfected with of constructed luciferase vectors (50 ng) and miR-100 mimic or mimic NC (50 nM) by Lipofectamine 2000. After 48 h incubation, the Dual-Glo Luciferase assay system (Promega) was chosen to assess the luciferase activity.

**Statistical analysis**

All experiments were conducted thrice. Data were displayed as mean ± standard deviation (SD). Student’s t-test was chosen for the evaluation of differences between two groups, and one-way ANOVA was adopted for the assessment of multiple groups. All data were analyzed using Graph Prism 6.0 software (GraphPad Prism, San Diego, CA). p < .05 was chosen as statistically significant.

**Results**

**Expression of HAGLROS is increased in cell lines of mantle cell lymphoma**

We firstly detected the HAGLROS expression in mantle cell lymphoma cell lines. Data revealed that HAGLROS level was high in five cell lines (Z-138, Mino, REC-1, Jeko-1, and JVM2) compared to that in normal B lymphocytes (P < .05, Figure 1A). Mino cell line had the highest expression level of HAGLROS among the five kinds of cell lines, which was used in the following experiments. Subsequently, HAGLROS was silenced in Mino cells by transfection. The expression of HAGLROS was markedly decreased in both sh-HAGLROS#1- and sh-HAGLROS#2-
transfected Mino cells relative to the corresponding sh-NC controls \( (p < .05, \text{Figure 1(B)}) \). sh-HAGLROS#1 was chosen for silence tests due to the higher transfection efficiency.

**Silencing of HAGLROS inhibits cell viability, increases apoptosis but decreases autophagy in mino cells**

We then investigated the influences of HAGLROS silencing on cell biological processes including viability, apoptosis and autophagy. HAGLROS suppression remarkably inhibited cell viability \( (p < .05, \text{Figure 1(C)}) \), enhanced apoptosis by accelerating the levels of apoptotic proteins of Bax/Bcl-2, p/t-caspase-3 and p/t-caspase-9 \( (p < .05, \text{Figure 1(D,E)}) \), but inhibited autophagy by increasing p62 expression and decreasing the levels of LC3-II/I and beclin-1 \( (p < .05, \text{Figure 1(E)}) \).

**Impacts of HAGLROS silencing on mino cell biological performances are by sponging miR-100**

There was a study reporting the interaction between HAGLROS and miR-100 \[14\], we thus speculated that HAGLROS might play a key role in lymphoma by sponging miR-100. We firstly detected the miR-100 expression in mantle cell lymphoma cell lines and found that miR-100 expression was obviously low in five mantle cell lymphoma cell lines (Z-138, Mino, REC-1, Jeko-1, and JVM2) compared to that in normal B lymphocytes \( (p < .05, \text{Figure 2(A)}) \). Moreover, miR-100 in sh-HAGLROS#1-transfected Mino cells was significantly higher than the sh-NC transfected Mino cells \( (p < .05, \text{Figure 2(B)}) \), indicating the inverse relevance between HAGLROS and miR-10. Afterwards, we successfully overexpressed and suppressed the expression of miR-100 in Mino cells by co-transfection of miR-100 mimic + miR-100 inhibitor, respectively \( (p < .05, \text{Figure 2(C)}) \). To further grab if HAGLROS contributed to lymphoma process via regulating miR-100, Mino cells were co-transfected with sh-HAGLROS#1 + miR-100 inhibitor. We found that combined transfection of sh-HAGLROS#1 + miR-100 inhibitor significantly reversed the effects of sh-HAGLROS#1 transfection alone on the viability \( (p < .05, \text{Figure 2(D)}) \), apoptosis \( (p < .05, \text{Figure 2(E,F)}) \) and autophagy \( (p < .05, \text{Figure 2(G)}) \) of Mino cells, reflecting the impacts of HAGLROS silencing on Mino cell biological performances was by sponging miR-100.
ATG5 is a target of miR-100

Using TargetsCanHuman, ATG5 was selected as a potential target of miR-100 (http://www.targetsCan.org/cgi-bin/targetsCan/vert_71/), and the complementary pairing sequence of them was presented in Figure 3(A). We found that only the luciferase index of pGL3-ATG5-wt was dramatically depressed by miR-100 mimic \( (p < .05, \text{Figure 3B}) \), reflecting that miR-100 could target ATG5. Moreover, the ATG5 level was markedly reduced by miR-100 mimic and increased by miR-100 inhibitor, respectively, which was consistent with the results of luciferase assay. These findings indicated that miR-100 could negatively regulate ATG5 expression.

**Figure 2.** Effects of HAGLROS silencing on Mino cell viability, apoptosis and autophagy by sponging miR-100. (A) miR-100 was decreased expressed in mantle cell lymphoma cell lines; (B) inverse expression between HAGLROS and miR-100; (C) miR-100 was successfully overexpressed and suppressed by transfection with miR-100 mimic and miR-100 inhibitor, respectively; (D–F) Mino cells were co-transfected with sh-HAGLROS#1 or sh-NC and miR-100 inhibitor or inhibitor NC, and their combined effects on the viability (D), apoptosis (E, F) and autophagy (G) of Mino cells. The experiments were repeated three times and the data are presented as mean ± SD. \* \( p < .05 \), \** \( p < .01 \), \*** \( p < .001 \) compared to the corresponding control group.
Figure 3. ATG5 was a target of miR-100 (A, B) and ATG5 expression was negatively regulated by miR-100 (C, D). The experiments were repeated three times and the data are presented as mean ± SD. *p < .05, and **p < .01 compared to the corresponding control group.

Figure 4. Effects of miR-100 overexpression on Mino cell viability, apoptosis and autophagy are by targeting ATG5. (A) ATG5 was successfully overexpressed and knocked down in Mino cells by transfection with pcDNA-ATG5 and si-ATG5, respectively; (B–E) Mino cells were co-transfected with miR-100 mimic or mimic NC and pcDNA-ATG5 or pcDNA3.1, and their combined effects Mino cell viability (B), apoptosis (C, D), and autophagy (E). The experiments were repeated three times and the data are presented as mean ± SD. *p < .05, **p < .01, ***p < .001 compared to the corresponding control group.
decreased in miR-100 mimic-transfected Mino cells and remarkably up-regulated in miR-100 inhibitor-transfected Mino cells \((p < .001, \text{Figure 3(C) and 3D})\), implying that ATG5 expression was negatively regulated by miR-100.

**Influences of miR-100 mimic on mino cell biological performances are by targeting ATG5**

We further verified whether miR-100 was involving in Mino cell biological performances via targeting ATG5. By transfection with pcDNA-ATG5 and si-ATG5, respectively, ATG5 was overexpressed and suppressed in Mino cells (Figure 4(A)). We then detected the combined effects of co-transfection of miR-100 mimic \(\text{þ} \text{pc-ATG5} \) on Mino cell viability, apoptosis and autophagy. And found that overexpression of miR-100 markedly inhibited Mino cell viability \((p < .05, \text{Figure 4(B)})\), promoted apoptosis by enhancing the protein levels of Bax/ Bcl-2, p/t-caspase-3 and p/t-caspase-9 \((p < .05, \text{Figure 4(C,D)})\), but inhibited autophagy via increasing p62 level and decreasing the level of LC3-II/I and beclin-1 \((p < .05, \text{Figure 4(E)})\), which were markedly changeover after co-transfection of miR-100 mimic \(\text{þ} \text{pc-ATG5} \) \((p < .05, \text{Figure 4(B–E)})\).

**PI3K/AKT/mTOR signal is a possible principle in mediating HAGLROS in mino cells**

The brisky PI3K/AKT/mTOR signal is widely involved in various physiological and pathological conditions (e.g. cancer), and this pathway is recently considered as a promising objective for cancer therapy [15,16]. The findings in this research revealed that HAGLROS suppression markedly resulted in the levels of p/t-PI3K, p/t-AKT, and p/t-mTOR \((p < .05, \text{Figure 5(A,B)})\), reflecting that silencing of HAGLROS depressed the briskness of PI3K/AKT/mTOR signals. Concurrently HAGLROS suppression and miR-100 inhibitor markedly altered the influences of HAGLROS suppression alone on the briskness of PI3K/AKT/mTOR signals, which could further change again after co-transfection of si-HAGLROS \(\text{þ} \text{miR-100 inhibitor} \text{þ} \text{si-ATG5} \) \((p < .05, \text{Figure 5(C)})\).

**Discussion**

This research uncovered that the expression of HAGLROS was increased in mantle cell lymphoma cell lines. Silencing of HAGLROS significantly inhibited Mino cell viability, increased apoptosis and decreased autophagy. Moreover, the impacts of HAGLROS on Mino cell viability, apoptosis and autophagy were possessed by miR-100/ATG5/PI3K/AKT/mTOR pathway. These data indicate that HAGLROS may promote the development of mantle cell lymphoma on the identity of oncogene, and targeting HAGLROS may be a potential therapy for this disease.

Multiple interaction networks including competing endogenous RNAs (ceRNAs) has been revealed, among which IncRNAs regulate the inhibitory effect of miRNA on mRNA
through competitively binding to miRNA [17,18]. Increasing pieces of evidence have revealed that HAGLROS regulated the malignant progression of tumour cells by competitively sponging miR-100 [11,12]. In line with these findings, our results also revealed that miR-100 was targeted by HAGLROS. In previous studies, down-regualtion of miR-100 is shown to be relevant to tumour metastasis and poor prognosis in colorectal cancer [19,20]. Moreover, the plasma level of miR-100 is found markedly decreased in bladder cancer patients, which could be a promising biomarker in clinical detection of bladder cancer [21]. Notably, it is reported that miR-100 is down-regulated in CD30+ primary cutaneous anaplastic large cell lymphoma samples compared to inflammatory dermatosis [22]. In this study, HAGLROS regulated the cell biological performances including viability, apoptosis and autophagy of Mino cells through negative regulation of miR-100. Although the role of miR-100 in mantle cell lymphoma remains incompletely understood, we deducted that HAGLROS may promote the process of this cancer by sponging miR-100.

In addition, there is increasing evidence that miRNAs are pivotal in tumourigenesis through targeting genes [23–26]. Our results revealed that ATG5 was targeted by miR-100. ATG5 is first identified in Burkitt’s lymphoma apoptotic cells [27]. Up-regulation of ATG5 expression is shown to interact with cell invasion in colorectal cancer tissues [28]. Amaravadi et al. demonstrated that interstress of ATG5 in lymphoma cells is shown to augment cell death following p53 activation, imply that autophagy acts as a pathway in tumour cells [29]. This research revealed the impacts of miR-100 mimic on Mino cell viability, apoptosis and autophagy are by targeting ATG5. We, therefore, speculated that HAGLROS may be crucial in mantle cell lymphoma via sponging miR-100 to regulate ATG5 expression.

Furthermore, the PI3K/AKT/mTOR signal is involved in many biological processes including cell growth and survival under pathological conditions including cancer [15,16]. The NVP-BEZ235, a dual PI3K and mTOR inhibitor, is shown to exhibit anti-proliferative activity in mantle cell lymphoma cells [30], supporting that targeting PI3K/AKT/mTOR signals provides a promising therapeutic strategy for mantle cell lymphoma. Schatz also suggested that targeting PI3K/AKT/mTOR signals may function as a feasible strategy for the treatment of non-Hodgkin lymphoma [31]. In the current study, we found that silencing of HAGLROS inhibited the briskness of the PI3K/AKT/mTOR pathway. Concurrent silencing of HAGLROS and inhibition of miR-100 markedly reversed the impacts of silencing of HAGLROS alone on the briskness of PI3K/AKT/mTOR pathway, which could further be reversed again after silencing of HAGLROS, miR-100 inhibitor and si-ATG5 simultaneously. We thus infer that PI3K/AKT/mTOR signal is a possible mechanism mediating the impact of HAGLROS in the development of mantle cell lymphoma.

Taken together, our findings indicated that HAGLROS is increased expressed in mantle cell lymphoma cells and may function as an oncogene in mantle cell lymphoma. HAGLROS may promote tumour development by regulating miR-100/ATG5 axis and by involving PI3K/AKT/mTOR signals. This research may pave the way for a novel insight for illustrating the biology of mantle cell lymphoma.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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