

Effect of miR-184 and miR-205 on the tumorigenesis of conjunctival mucosa associated lymphoid tissue lymphoma through regulating RasL10B and TNFAIP8

Yu-Zhen Li¹, Pei Mou¹, Ya Shen¹, Lian-Di Gao², Xin-Xin Chen¹, Rui-Li Wei¹

¹Department of Ophthalmology, Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China

²Department of Nursing, Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China

Co-first authors: Yu-Zhen Li, Pei Mou, and Ya Shen

Correspondence to: Rui-Li Wei. Department of Ophthalmology, Second Affiliated Hospital of Naval Medical University, 415 Fengyang Road, Huangpu District, Shanghai 200003, China. ruiliwei@126.com

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Abstract

● **AIM:** To explore the effect of miR-184 and miR-205 on the proliferation and metastasis of conjunctival mucosa associated lymphoid tissue (MALT) lymphoma.

● **METHODS:** Tissue of tumor and adjacent normal control from 5 patients with conjunctival MALT was included. RPMI8226 cell line was selected to verify the effect of miRNAs in B cells. The function of microRNA on the RPMI8226 cell apoptosis, migration and invasion was evaluated by apoptosis assay and Transwell assay. The mRNA and protein expression were examined by quantitative RT-PCR and Western blotting. The effect of microRNA on regulation of downstream gene expression was evaluated by luciferase report assay.

● **RESULTS:** A decreased level of miR-184 and miR-205 was observed in MALT lymphoma tissue. Exogenous miR-184 and miR-205 analogues promoted apoptosis, and inhibited the survival, migration, and invasion of RPMI8226 cells. miR-184 and miR-205 inhibitor reversed the process. The RNA and protein level of RasL10B and TNFAIP8 were downregulated in MALT lymphoma tissue. The exogenous of miR-184 and miR-205 promoted the expression of RasL10B and TNFAIP8. Meanwhile, inhibition of miR-184 and miR-205 repressed the expression of target gene, RasL10B and TNFAIP8.

● **CONCLUSION:** miR-184 and miR-205 suppresses the tumorigenesis of conjunctival MALT lymphoma through regulating RasL10B and TNFAIP8.

● **KEYWORDS:** mucosa associated lymphoid tissue lymphoma; microRNA; migration; RasL10B; TNFAIP8

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INTRODUCTION

Ocular adnexal lymphoma (OAL) is the most common tumors in the eyes. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), as a rare form of non-Hodgkin's lymphoma, is the majority subtype of OAL^[1]. The OAL causes a serious threaten to patient health. Therefore, the development of novel target drug is important for patients with OALs. However, the pathological mechanism of OALs is not clearly. MicroRNAs (miRNAs), as a group of short non-coding RNA molecules with 21-25 nucleotides length, regulate target gene translation or degradation through interacting with complementary sites in the 3' untranslated region (3'UTR) of target mRNAs^[2]. Increasing evidences indicated that miRNAs were involved in the pathogenesis of MALT lymphoma^[2-5]. miR-142 and miR-155 regulate the MALT pathogenesis through repressing the target gene TP53INP1^[4]. The decreased expression of miR-34a induces the target genes increase, such as FOXP1, p53, and BCL2, to regulate MALT lymphoma development and apoptosis^[6]. miR-200 is up-regulated and suppressed the target protein cyclin E2 in conjunctival MALT lymphoma^[2].

Previous studies indicated that miR-205 and miR-184 were involved in tumor proliferation, apoptosis, invasion, and metastasis. miR-205 acts as tumor activator or suppressor in various types of tumor *via* targeting various genes^[7-10]. The increased miR-205 expression promotes the proliferation, invasion, and migration of nasopharyngeal carcinoma cells^[7]. In renal cell carcinoma cells, miR-205 expression is decreased. In renal cell carcinoma cells, PTEN expression is upregulated and p-AKT expression is downregulated after the miR-205

mimics transfection^[10]. Previous studies indicated that miR-184 inhibits tumor cells proliferation and invasion in glioma and non-small cell lung cancer cells^[11-12]. Our previous study indicated that the expressions of miR-205 and miR-184 were decreased greatly in MALT tissue compared with control tissue^[2]. However, the mechanism of miR-205 and miR-184 regulating MALT lymphoma was not clear.

MATERIALS AND METHODS

Ethical Approval The Committee of Second Military Medical University biotechnology ethics reviewed. Samples were got followed the Helsinki Declaration. The samples were from conjunctival MALT lymphoma patients who signed the informed consent.

Clinical Specimens Five samples of tumor tissue from patients (4 males and 1 female, mean age 60.6±12.2y, range 40 to 71y, the onset time of 3mo to 6y) with conjunctival MALT lymphoma in this study were collected in Shanghai Changzheng Hospital from July to October in 2016, during anterior open acquisition orbital tumor surgery for MALT lymphoma. The matched adjacent normal conjunctival tissues as controls were obtained and were snap-frozen for further analysis. All patients had no other diseases except MALT lymphoma.

Cell lines Culture Human B cell line RPMI8226 (ATCC, Rockville, MD, USA) were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and maintained at 37°C in a humidified atmosphere containing 5% CO₂. The HEK cell line is a commonly used model cell which has a relatively high transfection rate, while the RPMI8226 cell line, a commonly used human B cell line, is utilized to verify the effect of miRNAs on B cells.

Apoptosis Assay RPMI8226 cells were planted 1.0×10⁶ cells per well in 6-well plates. When culturing to 50% confluence, miR-184 and miR-205 mimics or their negative control were transfected into cells carried by Lipofectamine 2000, respectively. Cell apoptosis was examined by the Annexin V-FITC/PI apoptosis detection kit, and detected by a flow cytometer and Cell Quest Pro version 6.0 software (FACScan; BD Biosciences, Franklin Lakes, NJ, USA).

Migration and Invasion Assays Transfected cells were gathered and then suspended. For the next step, 5×10⁴ or 1×10⁵ of the cells were planted onto the upper part of Transwell chambers (Corning, NY, USA), along with or without Matrigel covering (BD Biosciences, San Diego, CA, USA). Ten percent of FBS was added into the media and placed into the underlying part as a chemo attractant. Twelve or twenty-four hours later, cells migrated or invaded into the underlying part were recorded by an inverted microscope (Olympus, Tokyo, Japan).

RNA Extraction and Quantitative RT-PCR Total RNA was collected by TRIzol reagent (Invitrogen). M-MLV

reverse transcriptase (RT; Promega, Madison, WI, USA) was then used to reverse-transcribe. RT primers for miR-205 or random primers (Promega) for TNFAIP8 were from RiboBio (Guangzhou, China). Bio-Rad CFX96 Touch sequence detection system (Bio-Rad Laboratories Inc, Hercules, CA, USA) was used to conduct the quantitative polymerase chain reaction (qPCR) reactions. Platinum SYBRGreen qPCR SuperMix-UDG reagents (Invitrogen) were added into the reaction. Experiments were done three times. U6 or GAPDH were setting as controls. Primers used for qPCR were as followed: Urp-re-R2: 5'-GTGCAGGGTCCGAGGT-3', miR182-loop-2: 5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAGAGTGTG-3', miR182-re-F-2: 5'-CGGCGTTTGGCAATGGTAGAAC-3', miR205-loop-2: 5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCACAGAC-3', miR205-re-F-2: 5'-CGGCGTCCTTCATTCCACCG-3', RasL10B-F: 5'-GGGGGTACCATGGTCTCCACC-3', RasL10B-R: 5'-GCGGGATCCGCTCGGCCAG-3', TNFAIP8-F: 5'-TTCCATCAGGTGGATTATAC-3', TNFAIP8-R: 5'-AGGTGGCGCTGAATGATTTG-3'.

Western Blotting Analysis RPMI8226 cells were transfected with miR-205 mimics, miR-205 inhibitor or negative control miRNA using INTERFER in transfection reagent following the manufacturer's instructions (Polyplus). Whole cell extracts for immunoblotting analysis were prepared as previously reported. These antibodies were used for immunoblotting studies: rabbit anti RASL10B (1:500, Abbkine), rabbit anti TNFAIP8 (1:1000, Sigma), rabbit anti GAPDH (1:10 000, Sigma), goat anti rabbit IgG-HRP (1:6000, Millipore).

Luciferase Report Assay The psiCHECK-2 luciferase reporter plasmid (Promega) carried the cloning RASL10B WT and Mt 3'UTR, TNFAIP8 WT and Mt 3'UTR. Cells were first planted into six-well plates. One day later, cells were co-transfected using Lipofectamine 2000 reagent (Invitrogen), with the following: RASL10B WT or Mt 3'UTR reporter plasmids and miR-184 mimic, TNFAIP8 WT or Mt 3'UTR reporter plasmids and miR-205 mimic, and also the control vector pRL-TK (Promega). For the activities of luciferase, results were measured using the Dual-Luciferase Reporter Assay System (Promega). The primers used in luciferase assay as followed: Rasl10b WT-F: 5'-TCGAGCAGCCTTAACTCGATGGTCCGTCCCTGCCAGGTGCCGC-3', Rasl10b WT-R: 5'-GGCCGCGGCACCTGGCAGGGACGGACCATCGAGTAAAGGCTGC-3'; Rasl10b Mut-F: 5'-TCGAGCAGCCTTAACTCGATGGAGGCAGCCTGCCAGGTGCCGC-3', Rasl10b Mut-R: 5'-GGCCGCGCACCTGGCAGGCTGCCTCCATCGAGTTAAGGCTGC-3'; TNFAIP8 WT-F: 5'-TCGAGAAGATGGAGCACTGCTGATTTATGAAGGAAAAAAGAGC-3', TNFAIP8 WT-R: 5'-GGCCGCTCTTTTTTCCTTCATAAAT

CAGCAGTGCTCCATCTTC-3'; TNFAIP8 Mut-F: 5'-TCGAGAAGATGGAGCACTGCTGATTTTACTTCGAAAAAAGAGC-3', TNFAIP8 Mut-R: 5'-GGCCGCTCTTTTTCGAGTAAAATCAGCAGTGCTCCATCTTC-3'; Rasl10b WT-F: 5'-CAGCCUUAACUCGAUGGUCCGUCCUGCCAGGUGCC-3', Rasl10b Mut: 5'-CAGCCUUAACUCGAUGGAGGCAGCCUGCCAGGUGC-3'; TNFAIP8-WT: 5'-AAGAUUGGAGCACUGCUGAUUUUAUGAAGGAAAAAAGA-3', TNFAIP8-Mut: 5'-AAGAUGGAGCACUGCUGAUUUUACUUCGAAAAAAGA-3'.

Statistical Analysis All statistical analysis were completed by the SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Difference of measurement data was compared with *t*-test or one-way ANOVA. $P < 0.05$ were considered statistically significant.

RESULTS

Expression of miR-184 and miR-205 in MALT Lymphoma Tissue RNA was extracted from tumor tissues and adjacent tissues of 5 patients with MALT, and the mRNA expression of miR-184 and miR-205 was detected by qRT-PCR. The results showed that the expression of miR-184 and miR-205 mRNA were significantly downregulated in the lymphoma tissues compared with the adjacent tissues ($P < 0.001$; Figure 1).

Effect of miR-184 and miR-205 on the Proliferation and Apoptosis of RPMI8226 Cells In order to study the effect of miR-184 and miR-205 on the proliferation of lymphoma cells, miR-184 mimics and corresponding negative controls were transfected into the RPMI8226 cells. The CCK8 kits were used after transfection of 24, 48, 72, and 96h, and the value with 450 nm wavelength was detected. The results showed that the transfection of miR184 mimics notably inhibited the proliferation rate of RPMI8226 cells than the negative group. A similar result was observed when miR-205 mimics was transfected into the RPMI8226 cells. The results showed that the proliferation rate of RPMI8226 cells was significantly inhibited after transfected with miR-205 mimics than with the negative group. These results indicate that miR-184 and miR-205 notably inhibit the proliferation of RPMI8226 cells.

Then, the effect of miR-184 and miR-205 on the apoptosis of lymphoma cells was explored by flow cytometry. The results showed that the apoptosis rate was $0.06\% \pm 0.006\%$ in normal RPMI8226 cells group, and the rate was $1.2\% \pm 0.73\%$ in negative control group. Apoptosis rate was $12.4\% \pm 0.32\%$ in miR-184 mimics treated group, and the rate of the miR-205 mimics treated group was $17.1\% \pm 0.42\%$. Compared with normal group and negative control group, miR-184 and miR-205 mimics induced the apoptosis rate of RMPI8226 cells increased significantly (Figure 2; $P < 0.001$).

Effect of miR-184 and miR-205 on the Migration and Invasion of RPMI8226 Cells The effect of miR-184 and

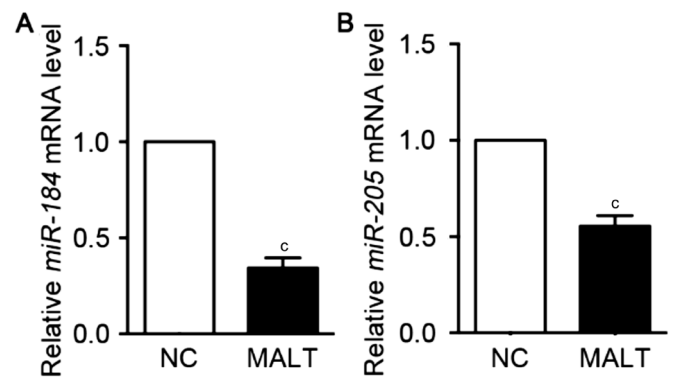


Figure 1 The miR-184 and miR-205 levels in MALT lymphoma tissues by qRT-PCR A: The miR-184 levels in MALT lymphoma tissues and negative control; B: The miR-205 levels in MALT lymphoma tissues and negative control. $n=5$, data showed as mean \pm SEM. ^c $P < 0.001$.

miR-205 on migration of RPMI8226 cells were examined by Transwell assay. The results showed that comparison to the negative group (100%), the number of migrated cells was the $118\% \pm 4.9\%$ in the miR-184 inhibitor treated group. However, the number of migrated cells only was $61.4\% \pm 12.7\%$ in the miR-184 mimics treated group (Figure 3A, 3C). Comparison to the negative control group (100%), the number of migrated cells in miR-205 inhibitor treated group was $110.7\% \pm 4.5\%$, while the number of migrated cells in the miR-205 mimics treated group was only $53\% \pm 11.7\%$ (Figure 3B, 3D).

Furthermore, we detected the effect of miR-184 and miR-205 on the invasion of RPMI8226 cells. The results showed that comparison to the negative group, the number of invaded cells in the miR-184 inhibitor treated groups was $142.2\% \pm 21.3\%$, while the number in mimics treated group was only $68.1\% \pm 12.7\%$ (Figure 4A, 4C). After transfection of 72h, compared to the negative control group, the number of invaded cells in the miR-205 mimics treated group was only $59.2\% \pm 12\%$, while the number of miR205 inhibitor groups through the cells was $143.4\% \pm 24.1\%$ in the control group (Figure 4B, 4D). These results suggested that miR-184 and miR-205 attenuated the ability of migration and invasion of RPMI8226 cells.

Influence of miR-184 on the Expression of RasL10B in MALT Lymphoma Previous study has shown that RasL10B may be a downstream target protein of miR-184 which participates in the pathogenesis of MALT lymphoma. We detected the expression level of RasL10B in MALT lymphoma tissues by real-time qPCR and Western blotting. The results revealed that RasL10B mRNA and protein in MALT lymphoma were significantly decreased compared para-cancerous tissue (Figure 5A-5C). The results of luciferase test showed that after transfection of miR184 mimics, the luciferase expression was significantly reduced ($P < 0.01$) after

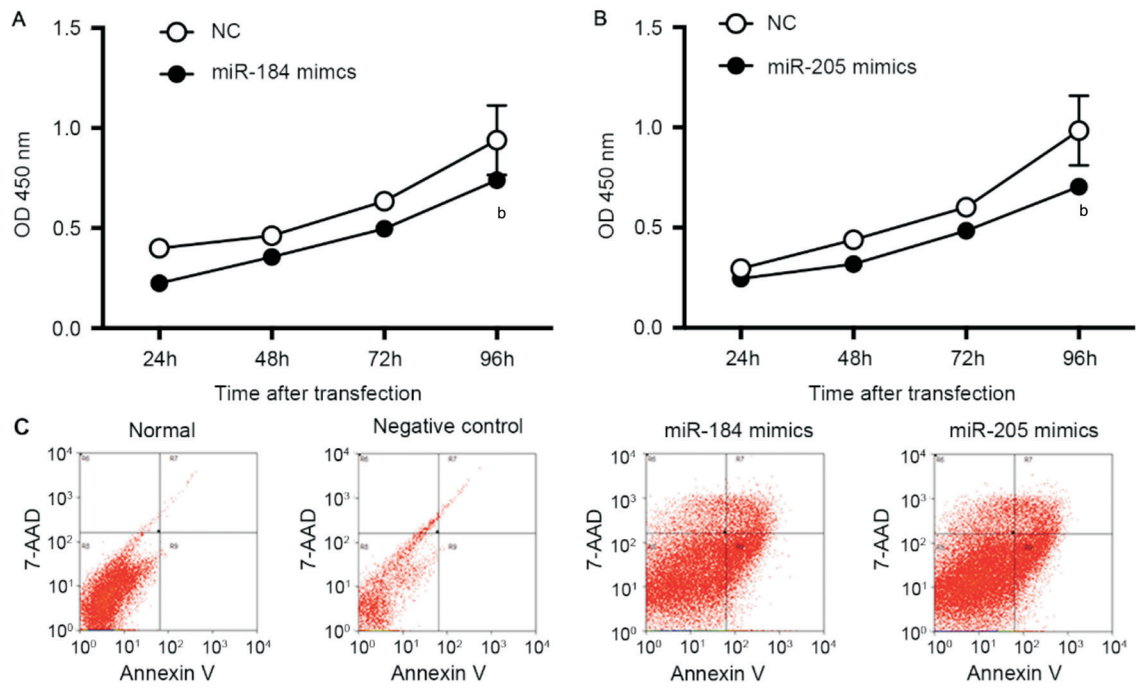


Figure 2 The proliferation and apoptosis of RPMI8226 cell after treatment of miR-184 and miR-205 mimics A: The proliferation curve of RPMI8226 cell after treatment of miR-184 mimics; B: The proliferation curve of RPMI8226 cell after treatment of miR-205 mimics; C: Apoptosis of RPMI8226 cells with the transfection of miR-184 and miR-205 mimics or the negative control, assessing by Annexin V-fluorescein isothiocyanate/PI staining. ^b $P < 0.01$ vs negative control. $n = 3$, data showed as mean \pm SEM.

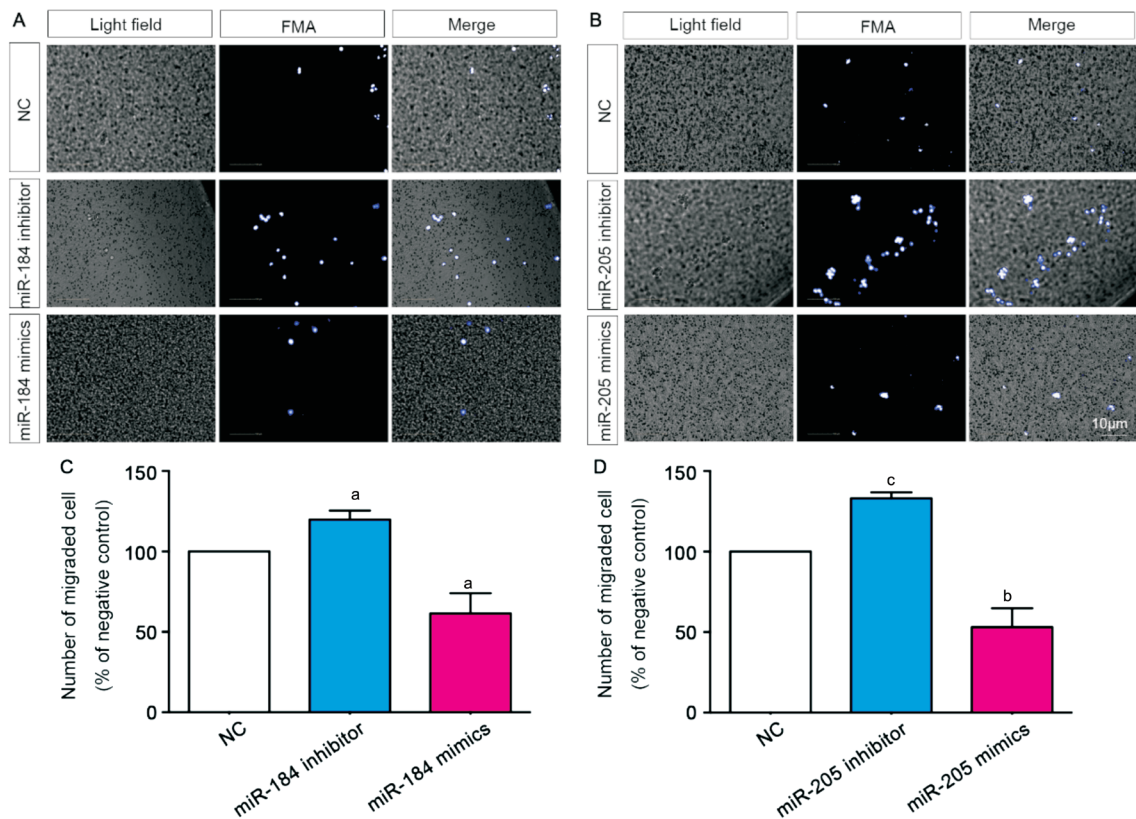


Figure 3 Effect of miR-184 and miR-205 mimics and inhibitor on the migration of RPMI8226 cells A: Recordings of RPMI8226 cells with the transfection of miR-184 mimics, inhibitor, or negative control in the underlying part of the Transwell assay for the assessing of cell migration; B: Recordings of RPMI8226 cells with the transfection of miR-205 mimics, inhibitor or negative control in the underlying part of the Transwell assay for the assessing of cell migration. C and D: Quantification of A and B. ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$ vs negative control. $n = 3$, data showed as mean \pm SEM.

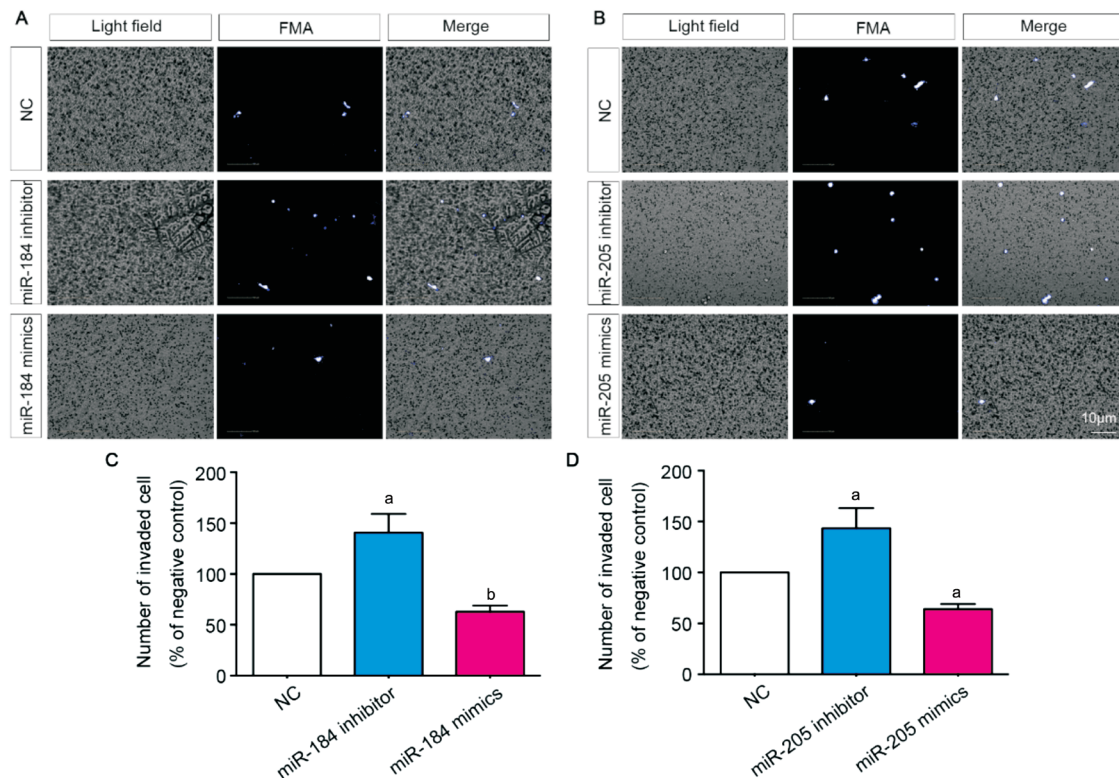


Figure 4 Effect of miR-184 and miR-205 mimics and inhibitor on the invasion of RPMI8226 cells A: Recordings of RPMI8226 cells with the transfection of miR-184 mimics, inhibitor or negative control in the underlying part of the Transwell assay for the assessing of cell invasion; B: Recordings of RPMI8226 cells with the transfection of miR-205 mimics, inhibitor or negative control in the underlying part of the Transwell assay for the assessing of cell invasion. C and D: Quantification of A and B, ^a $P < 0.05$, ^b $P < 0.01$ vs negative control. $n = 3$, the data was showed as mean \pm SEM.

transfection of the wild type RasL10B gene 3'UTR compared with the control group and the mutant group, indicating that miR184 has direct regulation on 3'UTR of the RasL10B gene (Figure 5D). In terms of the effect on the control group, the protein expression level of RasL10B was raised in RPMI8226 cells transfected to miR-184 mimics. However, miR184 inhibitor obviously decreased the expression level of RasL10B protein ($P < 0.05$; Figure 5E, 5F). These results suggested that miR184 can promote the gene expression of RasL10B in MALT lymphoma and RPMI8226 cells.

Regulation of miR-205 on RPMI8226 Cells through TNFAIP8 Previous study has shown that miR-205 participates in the tumor pathogenesis through regulating TNFAIP8. The expression level of TNFAIP8 mRNA and protein in MALT lymphoma were remarkably decreased compared with adjacent controls (Figure 6A-6C). The results of luciferase test showed that the luciferase expression significantly decreased after adding wild type TNFAIP8 gene 3'UTR compared with the control group and the mutant group (Figure 6D). The expression of TNFAIP8 protein was downregulated in RPMI8226 cells along with the transfection of miR-205 inhibitor by comparison to the negative group (Figure 6E, 6F). These results suggested that miR-205 can promote the gene

expression of TNFAIP8 in MALT lymphoma and RPMI8226 cells.

DISCUSSION

Dysfunctions of miRNAs are associated with many fields of tumor biology, such as tumor proliferation, apoptosis, and metastasis. miRNAs play bi-directional role as oncogenes or anti-oncogenes. Through previous research, we found that the expression level of miR-184 and miR-205 were abnormal in the MALT lymphoma tissue. In present study, we found a significantly decreased expression level of miR-184 and miR-205 in MALT tissues. In gain- and loss-of-function assay, miR-184 and miR-205 mimics suppressed the cellular proliferation, migration, and invasion of RPMI8226 cells and promoted the apoptosis of RPMI8226, while miR-185 and miR-205 inhibitor increased cellular migration and invasion. Luciferase assay and gain- and loss- of function assay indicated that miR-184 directly regulated target gene RasL10B and miR-205 regulated target gene TNFAIP8 in MALT lymphoma tissue and RPMI8226 cells. miR-184 and miR-205 could be a potential tumor suppressor of MALT lymphoma.

The abnormal expression of miR-184 and miR-205 in various types of tumor participates in tumor pathogenesis and progression. This study demonstrated that the expression

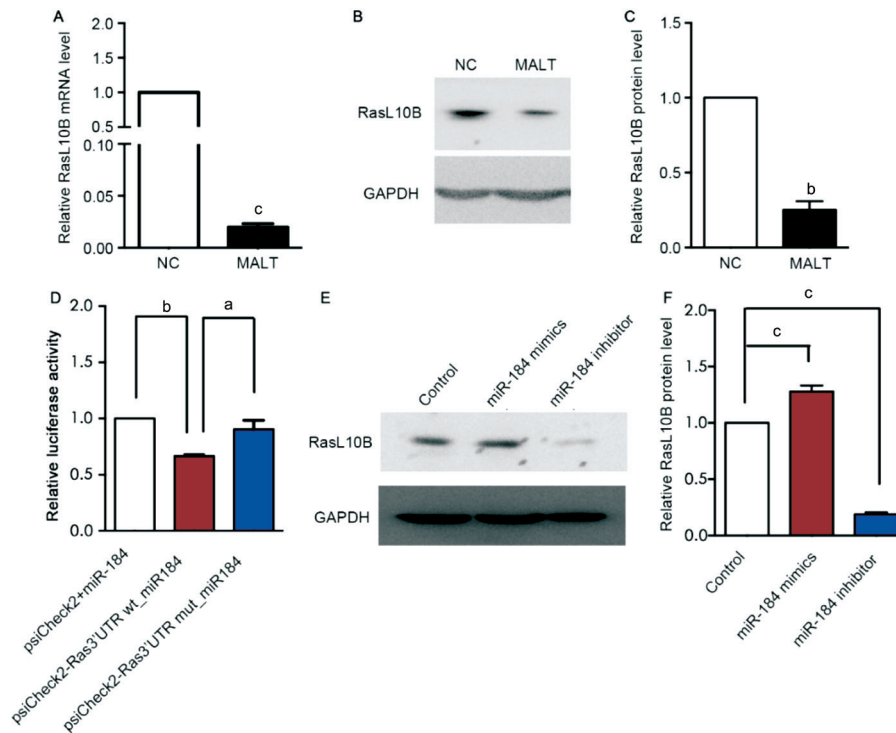


Figure 5 RasL10B was regulated by miR-184 in MALT and RPMI8226 cells A: The RasL10B mRNA in MALT lymphoma tissues, $n=5$; B: The RasL10B protein expression in MALT lymphoma tissues; C: Quantification of B, $n=3$; D: The wt-RasL10B/mut-RasL10B vectors and miR-184 mimics were co-transfected into RPMI8226 cells. The activity of luciferase of the RasL10B 3'UTR luciferase reporter vector was then determined, $n=3$, the data was showed as mean \pm SEM. E: The RasL10B protein expression in RPMI8226 cells treated with negative control, miR-184 mimics and miR-184 inhibitor; F: Quantification of B, $n=3$, the data was showed as mean \pm SEM. ^a $P<0.05$, ^b $P<0.01$, ^c $P<0.001$ vs negative control.

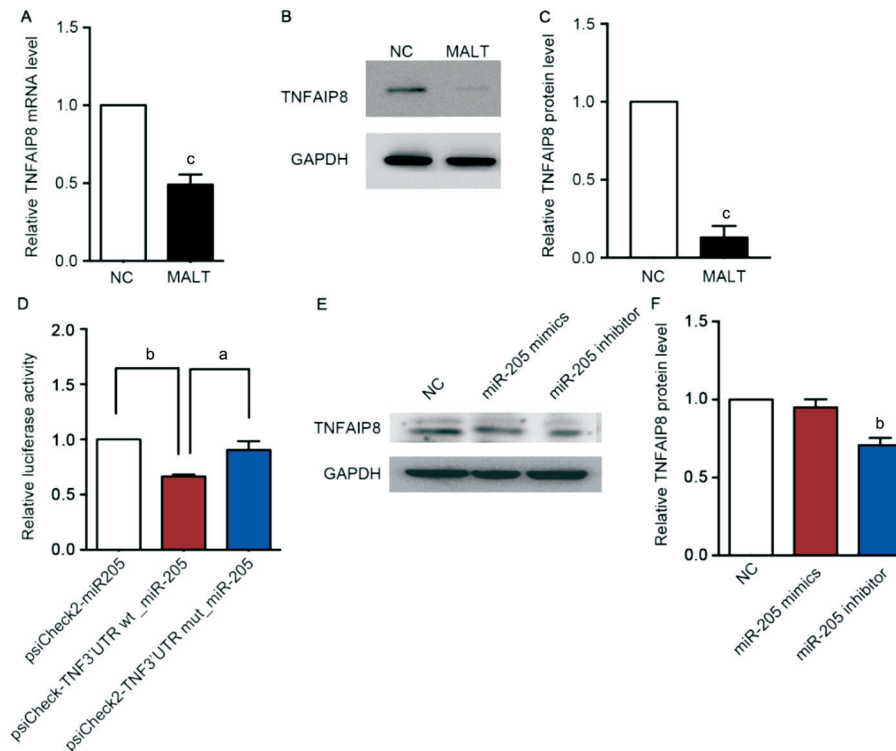


Figure 6 TNFAIP8 was regulated by miR-205 in MALT and RPMI8226 cells A: The TNFAIP8 mRNA in MALT lymphoma tissues, $n=5$; B: The TNFAIP8 protein expression in MALT lymphoma tissues; C: Quantification of B, $n=3$; D: The wt-TNFAIP8/mut-TNFAIP8 vectors and miR-205 mimics were co-transfected into RPMI8226 cells. The activity of luciferase of the TNFAIP8 3'UTR luciferase reporter vector was then determined, $n=3$, the data was showed as mean \pm SEM. E: The TNFAIP8 protein expression in RPMI8226 cells treated with negative control, miR-205 mimics and miR-205 inhibitor; F: Quantification of B, $n=3$, the data was showed as mean \pm SEM. ^a $P<0.05$, ^b $P<0.01$, ^c $P<0.001$ vs negative control.

of miR-184 and miR-205 in MALT lymphoma tissue were decreased compared with adjacent tissue.

miR-184 is involved in regulating the tumorigenesis and metastasis of tumor, as a new member of miRNA family. Previous research showed that the expression level of miR-184 was decreased in various types of tumor. In glioma tumor tissues, the expression of miR-184 was significantly decreased compared with normal brain tissue^[11]. In addition, Liang *et al*^[13] found that the level of miR-184 was reduced in central nervous system lymphoma. Meanwhile, the expression of miR-184 was found increased in other types of tumor. miR-184 was extensively expressed in PANC-1 cells, as a pancreatic ductal adenocarcinoma (PDAC) cell line^[14].

miR-205, as a conserved gene among multifarious species, is associated with tumor pathogenesis and progress. The expression of miR-205 is altered in different types of tumor tissue. In renal cell carcinoma, the expression level of miR-205 was downregulated compared with normal renal cells^[10]. Childs *et al*^[15] found that the low-level of miR-205 expression was a prognostic factor of head and neck squamous cell carcinoma. In other hand, previous studies showed that the expression level of miR-205 increased in some tumors. In human endometrial endometrioid carcinoma, the level of miR-205 was significantly increased^[8]. The altered expression of miR-184 and miR-205 suggest that miR-184 and miR-205 play various roles in different types of cancer.

miR-184 and miR-205 has opposite effect in various tumors through acting as an oncogene or an anti-oncogene. In some types of tumors, miR-184 and miR-205 promote the tumorigenesis and metastasis. It has been recently reported that miR-184 expression was increased in the osteosarcoma cells, and the miR-184 mimics enhanced the proliferation of osteosarcoma cells^[16]. Su *et al*^[8] found that when transfected with the miR-205 mimics, the proliferation, migration, and invasion ability of endometrial carcinoma tumor cells was upregulated. Nevertheless, our study demonstrated that miR-184 and miR-205 may be as a suppressor in the tumorigenesis and development of MALT lymphoma. In gain-and loss-of-function assay, miR-184 and miR-205 mimics reduced proliferation, migration and invasion of RPMI8226 cells, but promoted cellular apoptosis. Meanwhile, inhibition of miR-184 and miR-205 promoted the cellular migration and invasion. Our study is according with early studies in central nervous system lymphoma, renal cell carcinoma, and other tumors. Previous study showed that exogenous miR-184 suppressed the cell survival and invasion of central nervous system lymphoma, but miR-184 inhibitor could reverse the process^[13]. Wang *et al*^[10] found miR-205 mimics promote renal cell carcinoma cells apoptosis and inhibited the cellular proliferation and metastasis. In addition, the expression of

miR-205 suppressed the proliferation, migration and invasion of gastric cancer cells^[9].

In various types of tumor, miR-184 and miR-205 exerts their function through different target genes. To investigate the mechanism by which miR-184 and miR-205 exert their functions in MALT lymphoma, possible downstream target genes were focused. RasL10B is a member of Ras family, but its function remained unclear. Zou *et al*^[17] found that RasL10B was downregulated in breast tumor cells. Our results displayed similar results. In present study, the expression level of RasL10B was reduced in MALT tissue and RPMI8226 cells. Luciferase assay indicated miR-184 could directly regulate RasL10B 3'UTR. Furthermore, after treatment of miR-184 mimics, the RasL184 expression was inhibited in RPMI8226 cells, and miR-184 inhibitor reversed this process. These results suggest RasL10B as miR-184 downstream target protein, had suppressor potential in tumorigenesis and development. Excepted RasL10B, miR-184 modulated tumorigenesis *via* regulation of Wnt/ β -catenin signaling pathway in osteosarcoma^[18].

The deletion of TNFAIP8, which is expressed in lymphoid tissues, leads to multiorgan inflammation, splenomegaly, and premature death. Recently studies reported TNFAIP8 played an important role in tumor cell survival and apoptosis^[19]. Our results displayed that TNFAIP8 was decreased in MALT tissue and RPMI8226 cells compared with control group. Additionally, after treatment of miR-205 mimics, the TNFAIP8 expression was inhibited in RPMI8226 cells, and miR-205 inhibitor reversed this process. These results suggest that TNFAIP8 is miR-205 downstream target protein.

It has reported that miR-205 inhibited tumorigenesis and metastasis *via* PTEN/AKT pathway. In addition, miR-205 has been reported to regulate Smad4 and ubiquitin specific peptidase 7 in human non-small cell lung cancer and hepatocellular carcinoma^[20-21]. As we have revealed the role of miR-184/RasL10B and miR-205/TNFAIP8 in regulation of RPMI8226 cells, further investigation is needed to study the function of miR-184 and miR-205 *in vivo* in the tumor tissue and the downstream pathway regulated by miR-184 and miR-205. In conclusion, we revealed that the level of miR-184 and miR-205 mRNA in MALT was downregulated, and miR-184 and miR-205 analogues promote apoptosis of lymphoma RPMI8226 cells and attenuated the proliferation, migration, and invasion of RPMI8226 cells. The mRNA and protein level of RasL10B and TNFAIP8 were downregulated in MALT lymphoma tissue. miR-184 had direct regulation on the target gene RasL10B. Meanwhile, that the target gene TNFAIP8 was directly regulated by miR-205. Up of these suggested that miR-184 and miR-205 were presented as potential targets for the treatment of MALT lymphoma.

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