ISSN 1007-7626
CN 11-3870/Q
中国生物化学与分子生物学报 http://cjbmb.bjmu.edu.cn
Chinese Journal of Biochemistry and Molecular Biology
2018 年 9 月
34(9):997~1003

DOI: 10.13865/j.cnki.cjbmb.2018.09.12

MiR-150-5p 通过靶向调控 Rab1A 抑制乳腺癌细胞 MDA-231 的上皮-间质转化

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摘要 先前的研究表明,miR-150-5p 发挥抑癌基因的作用,调控肿瘤细胞的侵袭与转移。然而,关于其在乳腺癌细胞侵袭与转移中的机制尚不明确。本实验旨在研究 miR-150-5p 负向调控 Rab1A 在乳腺癌细胞上皮-间质转化(epithelial-mesenchymal transition,EMT)中的作用。双荧光素酶的结果显示,miR-150-5p 可负向调控 Rab1A。荧光定量 PCR (qRT-PCR) 结果显示,miR-150-5p 在乳腺癌细胞 MCF-7 及 MDA-MB-231(MDA-231)中的表达水平明显低于正常乳腺上皮细胞 MCF-10A;在 MDA-231 中过表达 miR-150-5p 后,qRT-PCR 结果显示,Rab1A mRNA 的表达水平明显降低。Western 印迹结果显示,过表达 miR-150-5p 后,miR-150-5p 组细胞中的 Rab1A、波形蛋白(vimentin)及 N-钙黏着蛋白(N-cadherin)的表达水平相对于对照组(NC)细胞明显降低,而 E-钙黏着蛋白(E-cadherin)的表达水平明显增加。Transwell 侵袭和划痕实验显示,与 miR-150-5p + Con 组细胞相比,miR-150-5p + Rab1A 组细胞的侵袭和迁移能力明显增加。qRT-PCR 结果显示,miR-150-5p + Rab1A 组细胞的 Rab1A mRNA 表达水平明显增加。Western 印迹结果显示,miR-150-5p + Rab1A 组细胞中的波形蛋白、N-钙黏着蛋白表达水平明显增加,而 E-钙黏着蛋白表达明显降低,过表达 Rab1A 后显著逆转了 miR-150-5p 对 EMT 的影响。综上所述,miR-150-5p 可以通过负向调控 Rab1A 抑制 EMT,进而抑制乳腺癌细胞的侵袭和迁移。

关键词 乳腺癌; miR-150-5p; Rab1A; 上皮-间质转化; 侵袭; 迁移

中图分类号 R737.9

Inhibition of Epithelial-mesenchymal Transition of MDA-231 Breast Cancer Cells by Targeted Regulation of Rab1A by miR-150-5p

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Abstract Previous studies have showed that miR-150-5p acts as a tumor suppressor gene and regulates the invasion and metastasis of tumor cells. However, its mechanism in the invasion and migration of breast cancer cells is unclear. The purpose of this study was to investigate the role of miR-150-5p in the negative regulation of Rab1A in epithelial-mesenchymal transition (EMT) of breast cancer cells. The results of double luciferase assay showed that miR-150-5p could negatively regulate Rab1A. The results

收稿日期: 2018-04-23; 修回日期: 2018-06-17; 接受日期: 2018-07-09
国家自然科学基金青年基金项目(No. 81702932, No. 81641111);山东省自然科学基金(No. ZR2015HL065)
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Received: April 23, 2018; Revised: June 17, 2018; Accepted: July 9, 2018
Supported by National Natural Science Foundation of China (No. 81702932, No. 81641111); Natural Science Foundation of Shandong Province (No. ZR2015HL065)
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of fluorescence quantitative real-time PCR (qRT-PCR) showed that the expression of miR-150-5p in breast cancer cells MCF-7 and MDA-MB-231 (MDA-231) was significantly lower than that in normal breast epithelial cells MCF-10 A. The result of qRT-PCR after overexpressing miR-150-5p in MDA-231 cells showed that the expression level of Rab1A mRNA was significantly increased. Western blotting showed that the expression level of Rab1A, Vimentin and N-cadherin were significantly decreased and the expression of E-cadherin was significantly increased in miR-150-5p-overexpression group cells compared with the control group cells. Transwell invasion and scratch assays revealed that the capacity of invasion and migration were obviously increased in miR-150- 5p + Rab1A group cells compared with miR-150-5p + Con group cells. qRT-PCR revealed that the expression of Rab1A mRNA was prominently increased in miR-150-5p + Rab1A group cells. Western blotting indicated that the expression levels of vimentin and N-cadherin were up-regulated in miR-150-5p + Rab1A group cells, but the expression of E-cadherin was down-regulated. Overexpressed Rab1A notably reversed the effects of miR-150-5p in EMT. In summary, these results illustrated that miR-150-5p suppresses EMT by targeting Rab1A, thus inhibiting the invasion and migration of breast cancer cells.

Key words breast cancer; miR-150-5p; Rab1A; epithelial-mesenchymal transition (EMT); invasion; migration

microRNAs (miRNAs) 是一类小的非编码的RNA序列,参与基因的转录后调控[1-2]。成熟的miRNAs主要是通过结合靶基因mRNA序列的3′非翻译区(3′UTR)调节基因的表达水平[3]。尽管大多数miRNAs的生物学功能尚未能揭示,但有报道发现,诸多miRNAs的差异性表达与乳腺癌的侵袭与迁移密切相关[4-5]。本实验室先前研究发现,miR-507可通过抑制Flt-1而抑制人乳腺癌的迁移与侵袭[6];垂体瘤转化基因1(pituitary tumor-transforming gene1, PTTG1)促进非小细胞肺癌的侵袭和迁移,且受miR-186的调控[7]。近来我们证实,miR-577可调控Rab25而抑制乳腺癌细胞上皮-间质转化(epithelial-mesenchymal transition,EMT)的发生和转移[8]。与此同时,本室发现Rab家族的Rab1A也可调控乳腺癌的侵袭与转移。本文通过靶向预测软件发现,miR-150-5p可结合Rab1A mRAN的3′非翻译区,且发现miR-150-5p调控Rab1A的表达。但是,关于miR-150-5p负向调控Rab1A在调节乳腺癌细胞侵袭和迁移的分子机制研究尚未见报道。本文通过转染单种质粒及共转染过表达miR-150-5p和过表达Rab1A质粒,检测其对乳腺癌细胞侵袭与迁移能力以及EMT标志物的影响,以此研究miR-150-5p在乳腺癌细胞侵袭和迁移中的作用机制。

1 材料与方法

1.1 材料

RIPA裂解液购自索莱宝;Matrigel购自BD公司;Transwell小室购自Corning公司;鼠抗人β-肌动蛋白单克隆抗体,兔抗人Rab1A多克隆抗体,兔抗人E-钙黏着蛋白单克隆抗体,兔抗人N-钙黏着蛋白多克隆抗体,兔抗人波形蛋白单克隆抗体购自Abcam公司;MEM、DMEM、RPMI1640培养基和胎牛血清购自美国Hyclone公司;所用质粒均购自吉凯公司;人乳腺癌细胞株MCF-7、MDA-231及正常乳腺上皮细胞株MCF-10 A购自ATCC。

1.2 细胞培养

人正常乳腺上皮细胞MCF-10 A,乳腺癌细胞MCF-7、MDA-231分别培养在含10% FBS的DMEM、MEM、RPMI1640培养基中。同时添加100 μg/mL青霉素和链霉素,于5% CO_2、37℃培养箱培养,实验前24 h不再添加抗生素。转染步骤参照Lipofectamine 2000操作说明。参照文献[8],细胞转染及共转染分组为:1)MDA-231组:常规培养,不做处理;2)Scr组:转入敲除Rab1A的对照质粒(GV248);3)SiRab1A组:转入敲除Rab1A质粒(GV248);4)NC组:转入过表达miR-150-5p的对照质粒(GV251);5)miR-150-5p组:转入过表达miR-150-5p质粒(GV251);6)miR-150-5p + Con组:同时转入过表达miR-150-5p质粒和过表达Rab1A的对照质粒(GV230);7)miR-150-5p + Rab1A组:同时转入过表达miR-150-5p和过表达Rab1A质粒(GV230)。

1.3 双荧光素酶

将Rab1A的3′-UTR的野生型(pGL3-Rab1A-3′UTR)和突变型(pGL3-Rab1A-3′UTR-mut)分别与对照质粒NC、过表达miR-150-5p质粒、对照质粒anti-NC、敲除miR-150-5p质粒(anti-miR-150-5p)进行共转染处理。该实验的操作过程参照文献[4]。

1.4　荧光定量 PCR

Trizol 法提取总 RNA,以 2 μg RNA 为模板进行逆转录。获得第一链 cDNA 后,分别用 Mir-X™ miRNA qRT-PCR SYBR® Kit 和 SYBR® Green I 染料进行 qRT-PCR。以 *U6*、*β*-肌动蛋白分别为内参。RT-PCR 结果分析采用 $2^{-\Delta\Delta CT}$, $\Delta CT_{(test)} = CT_{(target,\ test)} - CT_{(ref,\ test)}$, $\Delta CT_{(calibrator)} = CT_{(target,\ calibrator)} - CT_{(ref,\ calibrator)}$, $\Delta\Delta CT = \Delta CT_{(test)} - \Delta CT_{(calibrator)}$。反应条件参照文献[9]及 miR-150-5p 的茎环序列:5′-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCACTGG-3′,上游引物:5′- GCGTCTCCCAACCCTTGTA-3′,下游引物:5′ - AGTGCAGGGTCCGAGGTATT-3′。Rab1A 上游引物:5′-TCATGACGATGGCAGCTGAG-3′,下游引物 5′-TAGCAGCAACCTCCACCTGA-3′。

1.5　Western 印迹检测

MCF-10 A、MCF-7、MDA-231 细胞及转染后的各组细胞用 RIPA 裂解液裂解后进行蛋白质抽提。接着进行 12% SDS-PAGE,转膜,5% 脱脂奶粉封闭,孵育一抗 4℃过夜;第 2 d,TBST 洗膜,孵育二抗,再次 TBST 洗膜,添加 ECL 曝光。一抗浓度为:Rab1A(1∶1 000)、E-钙黏着蛋白(1∶1 000)、N-钙黏着蛋白(1∶1 000)、波形蛋白(1∶1 000)、β-肌动蛋白(1∶1 000)。

1.6　Transwell 侵袭检测

参照文献[10],取 150 μL 细胞悬液(2×10^5 个/mL)于小室上室中,下室加入含 20% FBS 的培养基。于培养箱中继续培养 24 h,用脱脂棉签擦去未消化的基质胶,并用 PBS 清洗干净,用 100% 甲醇固定细胞 5 ~ 10 min。Giemsa 染色 30 ~ 40 min,PBS 清洗,棉签擦拭。室温晾干后,于光镜下观察拍照。随机选取 10 个视野观察拍照计数,取平均值作为最终结果。

1.7　划痕实验

将各组转染后细胞以 2.5×10^5 个/每孔接种到 6 孔板中,继续培养 24 h。此时,细胞汇合度达到 70% ~80%。用 10 μL 的枪头在单层贴壁细胞中间画一条笔直的线。用 PBS 反复清洗 3 次,洗去未贴壁细胞,换入含 2% FBS 培养基。光镜下观察,分别在 0 h、24 h 拍照记录。结果用 ImageJ 软件计算细胞迁移的距离,计算方法参照文献[9]。

1.8　统计学分析

实验数据均采用 SPSS18.0 统计学软件进行处理,采用单因素方差分析或独立样本 *t* 检验进行统计学验证。所有数据采用(mean ± *SD*)表示,$P < 0.05$ 认为差异具有统计学意义。

2　结果

2.1　Rab1A 是 miR-150-5p 的直接作用靶点

通过 miRNAMap 和 Targetscan 两个预测软件获得 Rab1A 与 miR-150-5p 存在靶向结合位点。采用双荧光素酶检测 Rab1A 与 miR-150-5p 是否存在相互结合及调控。结果(Fig. 1)所示,miR-150-5p 可特异结合于 *Rab1A* 基因 mRNA 的 3′UTR,且两者间存在负向调控。

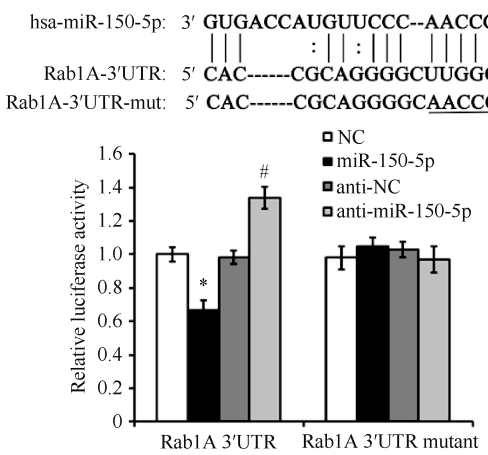

Fig. 1　Rab1 A was a direct target of miR-150-5p
Targetscan and miRNAMap were used to predict the binding site between miR-150-5p and Rab1A. The dual luciferase assay was employed to detect the relationship between miR-150-5p and Rab1A ($^*P < 0.05$, *vs.* NC; $^\#P < 0.05$, *vs.* anti-NC). This assay was repeated three times. Bars, standard deviation

2.2　miR-150-5p 在乳腺癌细胞中的表达降低

采用 qRT-PCR 检测 miR-150-5p 在正常乳腺上皮细胞 MCF-10 A,以及乳腺癌细胞 MCF-7 和 MDA-231 中的表达。同时检测过表达 miR-150-5p 后,其转染效率及 Rab1A mRNA 的表达水平。结果显示,miR-150-5p 在正常乳腺上皮细胞 MCF-10 A 的表达水平,明显高于乳腺癌细胞 MCF-7 和 MDA-231(Fig. 2 A);且相较于 NC 组,转染过表达 miR-150-5p 质粒后,MDA-231 中的 miR-150-5p 的表达水平明显上升,而 Rab1A mRNA 的表达水平明显下降(Fig. 2B)。

2.3　高表达 miR-150-5p 抑制了 EMT 的发生

Western 印迹检测转染 miR-150-5p 后对靶蛋白 Rab1A 及 EMT 标志物的影响。结果显示,与 NC 细胞组相比,miR-150-5p 细胞组中 Rab1A、N-钙黏着

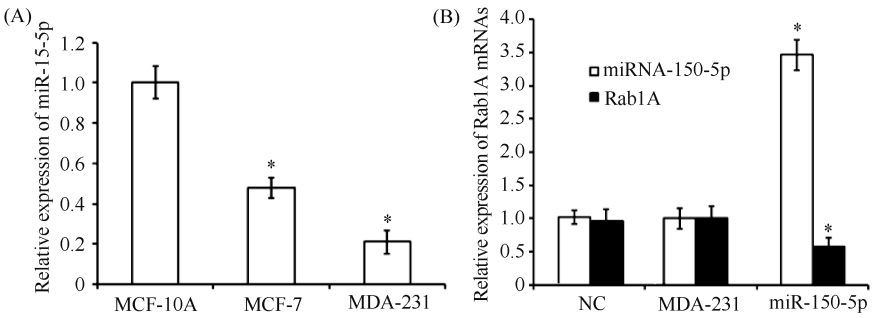

Fig. 2 The levels of miR-150-5p was attenuated in various breast cancer cells (A) The total RNA was extracted from MCF-10 A, MCF-7 and MDA-231cells by Trizol. QRT-PCR was employed to detect the expression levels of miR-150-5p in various breast cancer and normal cells ($^{*}P < 0.05$, *vs.* MCF-10 A); (B) The total RNA was extracted from MDA-231, NC and miR-150-5p group cells. QRT-PCR was employed to detect the expression levels of miR-150-5p and Rab1A mRNA in indicated cells ($^{*}P < 0.05$, *vs.* NC). U6 and β-actin were respectively used as a loading control. Bars, standard deviation. This assay was repeated three times

蛋白、波形蛋白的表达水平显著降低，而 E-钙黏着蛋白的表达水平明显增加(Fig. 3)。

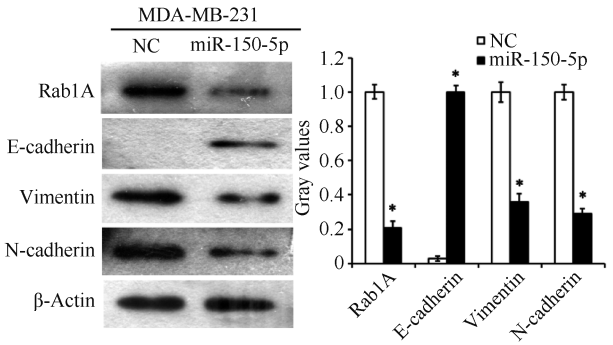

Fig. 3 Overexpressed miR-150-5p inhibited the process of EMT The total protein was extracted from NC and miR-150-5p group cells. The target protein Rab1A and EMT markers were detected by Western blotting. The quantification analysis of the expression levels of Rab1A, E-cadherin, N-cadherin and vimentin in NC and miR-150-5p group cells ($^{*}P < 0.05$, *vs.* NC). β-actin was used as a loading control. Bars, standard deviation. These results were repeated at least three times

2.4 过表达 Rab1A 逆转 miR-150-5p 对 MDA-231 细胞侵袭能力的抑制作用

为检测 miR-150-5p 对乳腺癌细胞 MDA-231 侵袭能力的影响，采用 Transwell 侵袭实验检测转染及共转染后 MDA-231 侵袭能力的变化。结果显示，与 miR-150-5p + Con 组细胞相比，miR-150-5p + Rab1A 组细胞穿过人工基底膜的细胞数明显增加($^{\#}P < 0.05$, Fig. 4B)。结果提示，过表达 Rab1A 逆转了 miR-150-5p 对 MDA-231 细胞侵袭能力的抑制作用。

2.5 过表达 Rab1A 逆转 miR-150-5p 对 MDA-231 细胞迁移能力的抑制作用

为进一步检测 miR-150-5p 对乳腺癌细胞 MDA-231 迁移能力的影响，划痕实验检测转染及共转染后 MDA-231 细胞迁移能力的变化。结果显示，与 miR-150-5p + Con 组细胞相比，miR-150-5p + Rab1A 组细胞迁移的距离明显增加($^{\#}P < 0.05$, Fig. 5B)。

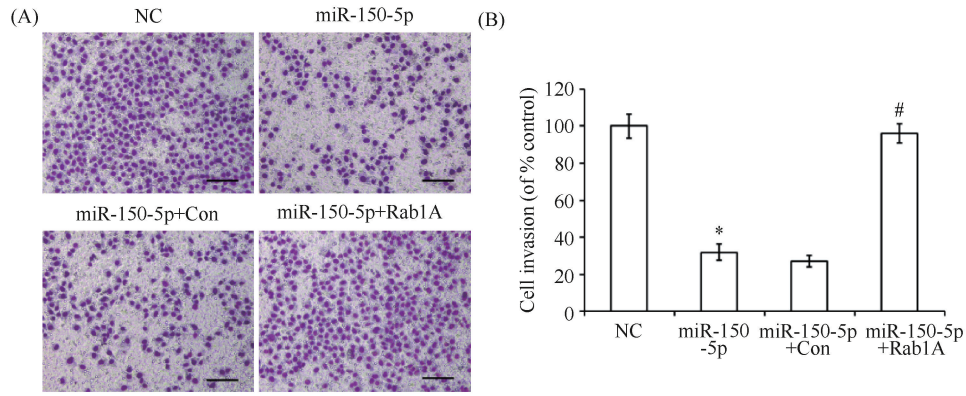

Fig. 4 Overexpressed Rab1A reversed the capacity of invasion triggered by miR-150-5p Transwell invasion assays were employed to assess the change of invasion capacity in the various breast cancer cell groups after transfection. (A) Images of penetrated NC, miR-150-5p, miR-150-5p + Con and miR-150-5p + Rab1A group cells; (B) Quantification analysis of Transwell invasion assays on NC, miR-150-5p, miR-150-5p + Con and miR-150-5p + Rab1A group cells ($^{*}P < 0.05$, *vs.* NC; $^{\#}P < 0.05$, *vs.* miR-150-5p + Con). Scale bar 200 μm. Bars, standard deviation. This assay was repeated three times

结果提示,过表达 Rab1A 逆转了 miR-150-5p 对 MDA-231 细胞迁移能力的抑制作用。

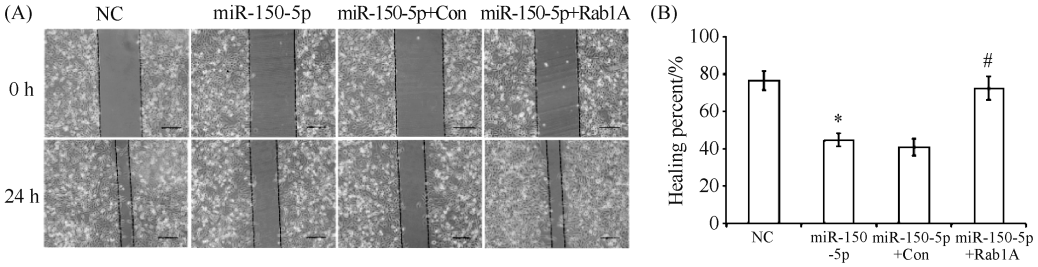

Fig. 5　Overexpressed Rab1A reversed the capacity of migration triggered by miR-150-5p　Scratch assays were employed to detect the change of migration capacity in the various breast cancer cell groups. (A) Images of migrated NC, miR-150-5p, miR-150-5p + Con and miR-150-5p + Rab1A group cells at 0 and 24 hours; (B) Quantification of scratch assays on NC, miR-150-5p, miR-150-5p + Con and miR-150-5p + Rab1A group cells ($^{*}P < 0.05$, *vs.* NC; $^{\#}P < 0.05$, *vs.* miR-150-5p + Con). Scale bar 200 μm. Bars, standard deviation. This assay was repeated three times

2.6　过表达 Rab1A 逆转 miR-150-5p 对 Rab1A mRNA 的下调

QRT-PCR 检测转染及共转染后各组 MDA-231 细胞中 Rab1A mRNA 表达水平的变化。结果显示,敲除 *Rab1A* 的 SiRab1A 组细胞和过表达 miR-150-5p 的 miR-150-5p 组细胞中 Rab1A mRNA 产生了相似的变化,相对于其对照组,Rab1A mRNA 的表达水平明显下降。与 miR-150-5p + Con 组细胞相比,过表达 Rab1A 后逆转了 miR-150-5p 对 Rab1A mRNA 的下调作用($^{\triangle}P < 0.05$, Fig. 6)。

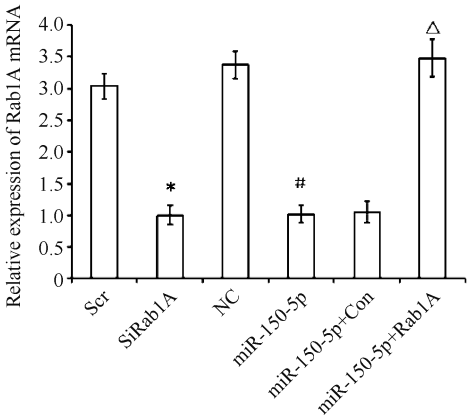

Fig. 6　Overexpressed Rab1A reversed the effects of Rab1A mRNA induced by miR-150-5p　The total RNA was extracted from Scr, SiRab1A, NC, miR-150-5p, miR-150-5p + Con, and miR-150-5p + Rab1A group cells, respectively by using Trizol. Quantification of Rab1A mRNA levels in those indicated group cells were analyzed ($^{*}P < 0.05$, *vs.* Scr; $^{\#}P < 0.05$, *vs.* NC; $^{\triangle}P < 0.05$, *vs.* miR-150-5p + Con). β-actin was used as a loading control. Bars, standard deviation. This assay was repeated three times

2.7　过表达 Rab1A 降低 miR-150-5p 对 EMT 的抑制

Western 印迹检测转染及共转染后各组细胞中 EMT 标志物表达水平的变化。结果显示,敲除 *Rab1A* 的 SiRab1A 组细胞和过表达 miR-150-5p 的 miR-150-5p 组细胞中 EMT 标志物产生了相似的变化。与此同时,与 miR-150-5p + Con 组细胞相比,miR-150-5p + Rab1A 组细胞中的波形蛋白、N-钙黏着蛋白表达水平明显增加,而 E-钙黏着蛋白的表达水平明显下降($^{\triangle}P < 0.05$, Fig. 7)。结果提示,过表达 Rab1A 降低 miR-150-5p 对 EMT 的抑制。

3　讨论

近年来,乳腺癌发病率逐渐升高且日趋年轻化[11-12]。随着对其发生机制及遗传学上的了解,尽管在治疗乳腺癌的方法和技术上获得了长远的发展。然而,一旦发生转移,患者死亡率大幅提升,且目前其分子机制尚不清楚[13-14]。因此,研究其侵袭与迁移的分子机制,将为临床治疗乳腺癌提供新的理论靶点。

Rab1A (Ras-related protein, Rab1A) 是小分子 GTP 结合蛋白质,具有 GTP 酶的活性,可以通过结合相关蛋白质参与和调节细胞的信号传导及自噬[15]。同时,它参与内质网和高尔基体间的膜泡运输过程[16]。近来发现,Rab1A 在诸多肿瘤细胞的侵袭与迁移中发挥重要的作用,例如:结肠癌[17]和肝癌[18]。同时,Rab1A 可通过 mTOR/ P70S6K 促进乳腺癌细胞的 EMT[19]。本文获得相同的结论,敲低 *Rab1A*,乳腺癌细胞的 N-钙黏着蛋白、波形蛋白显著下调,E-钙黏着蛋白上调。

miRNAs 的异常表达与肿瘤细胞的 EMT 密切相关。先前研究表明,linc00673 通过沉默 miR-150-5p 促进肺癌细胞的 EMT,进而加快肺癌细胞的增殖与侵袭[20]。同时,miR-150-5p 可分别靶向抑制 MMP-

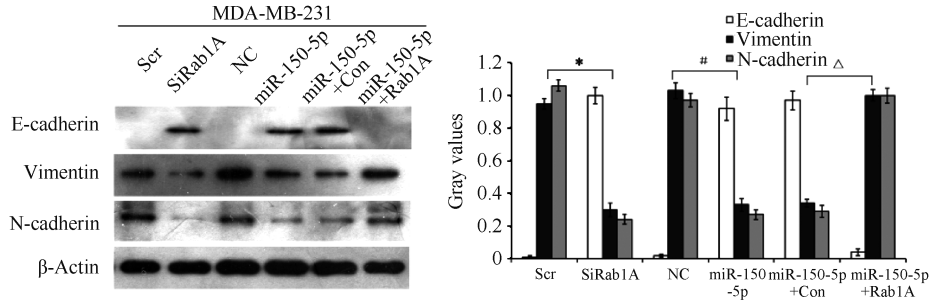

Fig. 7 Overexpressed Rab1A decreased the effects of EMT induced by miR-150-5p The total protein was extracted from Scr, SiRab1A, NC, miR-150-5p, miR-150-5p + Con, miR-150-5p + Rab1A group cells, respectively. The levels of E-cadherin, N-cadherin and vimentin were detected by Western blotting. Quantification of the expression levels of E-cadherin, N-cadherin and vimentin in those indicated group cells were analyzed ($^{*}P < 0.05$, *vs.* Scr; $^{\#}P < 0.05$, *vs.* NC; $^{\triangle}P < 0.05$, *vs.* miR-150-5p + Con). β-actin was used as a loading control. This assay was tested repeatedly at least three times. Bars, standard deviation

14、MT1-MMP 的表达,而抑制肺鳞癌[21]、胶质瘤的侵袭和迁移。Koshizuka 等[22-23]发现,miR-150-5p 靶向结合 SPOCK1,调控头颈鳞状细胞癌、食管鳞状细胞癌的侵袭。近来发现,miR-150-5p 可调节 EGR2 促进慢性病的发展[24]。本文同样发现,miR-150-5p 可调控乳腺癌细胞 EMT 的发生。双荧光素酶检测验证,Rab1A 是 miR-150-5p 的直接靶点。过表达 Rab1A 逆转了 miR-150-5p 对 Rab1A mRNA 的降低,且逆转了 miR-150-5p 对乳腺癌细胞侵袭、迁移及 EMT 的影响。揭示了 miR-150-5p、Rab1A、EMT 在乳腺癌细胞侵袭、迁移中的关系,证明了 miR-150-5p 通过靶向结合 Rab1A 调节乳腺癌细胞的 EMT,进而抑制侵袭和迁移。

综上所述,本研究证实,miR-150-5p 可以通过调控 Rab1A 靶蛋白抑制的 EMT 的发生,进而抑制乳腺癌细胞 MDA-231 的侵袭和迁移。因此,研究 miR-150-5p 和 Rab1A 在乳腺癌细胞侵袭、迁移中的作用机制,将为临床治疗乳腺癌提供一个新的思路与理论支撑。

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