DOI:10.3872/j.issn.1007-385x.2021.11.008

·临床研究·

miR-19通过靶向PTEN调节PI3K-Akt通路促进子宫内膜癌KLE细胞的侵袭和迁移

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[摘 要] **目的**:分析miR-19对PTEN及PI3K-Akt通路的调节作用,揭示miR-19和PTEN对子宫内膜癌KLE细胞侵袭、迁移的影响及其机制。**方法**:收集2017年5月至2020年8月河北医科大学第一医院收治的74例子宫内膜癌患者经手术切除(术前未接受放化疗等治疗)且病理确诊为子宫内膜癌的肿瘤组织及对应癌旁组织,采用qPCR和WB法检测PTEN在子宫内膜癌组织中的表达水平以及转染miR-19模拟物或抑制物对KLE细胞中PTEN表达的影响。通过TargetScan及双荧光素酶报告基因实验预测并验证PTEN是否为miR-19的靶基因,将KLE细胞随机分为对照(NC)组、miR-19模拟物组和miR-19+PTEN组,分别转染阴性对照片段(miR-NC)、miR-19模拟物或共转染miR-19模拟物+PTEN过表达载体,采用Transwell和细胞划痕实验检测miR-19和PTEN对KLE细胞迁移和侵袭能力的影响,WB法检测对PI3K-Akt通路相关蛋白表达的影响。**结果**:子宫内膜癌组织中PTEN的mRNA和蛋白表达水平均明显低于癌旁组织(均P<0.01)。miR-19能与PTEN mRNA的3'-UTR特异性结合,上调miR-19的表达能抑制PTEN的mRNA和蛋白的表达,下调miR-19的表达则出现相反的结果(均P<0.01)。与miR-NC组相比,miR-19模拟物组的迁移、侵袭细胞数以及划痕愈合率均显著升高(均P<0.01),而miR-19+PTEN组的细胞迁移和侵袭能力以及划痕愈合率较miR-19摸拟物组则明显降低(均P<0.01);与miR-NC组相比,miR-19模拟物组中PTEN蛋白的表达明显降低,而p-Akt 308和p-Akt 473蛋白的表达明显升高,Akt蛋白的表达无明显变化(均P<0.01);而在miR-19+PTEN组中,p-Akt 308和p-Akt 473蛋白的表达均明显低于miR-19模拟物组(均P<0.01)。**结论**:miR-19可能通过抑制PTEN的表达从而活化PI3K-Akt通路,进而促进子宫内膜癌KLE细胞的迁移和侵袭。

[关键词] 子宫内膜癌;miR-19;PTEN;KLE细胞;PI3K-Akt通路
[中图分类号] R737.33; R730.2 [文献标识码] A [文章编号] 1007-385X(2021)11-1107-06

miR-19 regulates PI3K/Akt signaling pathway by targeting PTEN to promote invasion and migration of endometrial cancer KLE cells

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[Abstract] Objective: To analyze the regulatory effects of miR-19 on PTEN and PI3K/Akt signaling pathway, and to reveal the effects of miR-19 and PTEN on invasion and migration of endometrial cancer KLE cells as well as its working mechanism. **Methods:** Tumor tissues and para-carcerous tissues of 74 patients with endometrial cancer were collected from the First Hospital of Hebei Medical University from May 2017 to August 2020. All patients did not receive radiotherapy or chemotherapy before surgery and were pathologically diagnosed as endometrial cancer. qPCR and WB were used to detect the effects of miR-19 mimics or inhibitors on PTEN expression in KLE cells. TargetScan and Dual-luciferase reporter gene assay were adopted to predict and verify whether PTEN was the target gene of miR-19. KLE cells were randomized into negative control (NC) group (transfected with miR-NC), miR-19 mimic group (transfected with miR-19 mimics) and miR-19+PTEN group (transfected with miR-19 mimics+PTEN overexpression vector). Transwell assay and Scratch assay were used to detect the effects of miR-19 and PTEN on KLE cell migration and invasion. WB was adopted to detect the expression of PI3K/Akt pathway-related proteins.**Results:** mRNA and protein expression of PTEN was obviously lower in endometrial cancer tissues compared with para-carcerous tissues (P<0.01). miR-19 could specifically bind to 3'-UTR of PTEN. Up-regulation of miR-19 could inhibit mRNA and protein expression of PTEN, and down-regulation of miR-19 showed an opposite

[基金项目] 河北省卫生厅科研基金项目青年科技计划资助(No. 20200126)。Project supported by the Youth Science and Technology Project of Scientific Research Foundation from the Department of Health of Hebei Province (No. 20200126)
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result (P<0.01). Compared with miR-NC group, migratory cell count, invasive cell count, and scratch healing rate were significantly increased in miR-19 mimic group (all P<0.01). Compared with miR-19 mimic group, migratory cell count, invasive cell count and scratch healing rate were significantly decreased in miR-19+PTEN group (all P<0.01). WB analysis showed that, comparing with miR-NC group, PTEN protein was obviously decreased, while p-Akt 308 and p-Akt 473 protein was obviously elevated in miR-19 mimic group (P<0.01); however, Akt protein maintained unchanged. Additionally, the levels of p-Akt 308 and p-Akt 473 protein were obviously lower in miR-19+PTEN group comparing with miR-19 mimic group (P<0.01). **Conclusion:** miR-19 may activate PI3K/Akt signal pathway by inhibiting PTEN expression, thereby promoting migration and invasion of endometrial cancer KLE cells.

[Key words] endometrial cancer; miR-19; PTEN; KLE cell; PI3K-Akt pathway

[Chin J Cancer Biother, 2021, 28(11): 1107-1112. DOI: 10.3872/j.issn.1007-385x.2021.11.008]

子宫内膜癌是女性生殖系统最常见的恶性肿瘤之一[1-3]。近年来，中国人子宫内膜癌发病率呈上升趋势，对于类型特殊、恶性程度高又易复发转移的病例，常规治疗效果较差[4-6]，因此寻找和发现子宫内膜癌相关调控基因对开发子宫内膜癌新的治疗靶点具有重要意义。PTEN是重要的抑癌因子，由于基因突变、缺失或启动子高度甲基化导致的PTEN沉默会诱发子宫内膜癌等癌症发生[7-9]。研究[10]显示，PTEN的下调与PI3K-Akt通路的激活有关，可促进肿瘤的发生发展。多种miRNA在子宫内膜癌中异常表达[11-12]，但关于miR-19在子宫内膜癌中的功能目前尚鲜有报道。本研究旨在观察miR-19对子宫内膜癌KLE细胞迁移和侵袭能力的影响，分析miR-19对PTEN及PI3K-Akt通路的调节作用，阐明miR-19在子宫内膜癌中的作用及其可能的机制。

1　材料与方法

1.1　组织标本、细胞及主要试剂

收集2017年5月至2020年8月河北医科大学第一医院收治的74例子宫内膜癌患者经手术切除（术前未接受放化疗等治疗）且病理确诊为子宫内膜癌的肿瘤组织及对应癌旁组织（距肿瘤边缘>5 cm），所有标本的收集均获得家属知情同意，并签署知情同意书，操作符合临床试验伦理规范。子宫内膜癌KLE细胞购自中国科学院上海细胞库，用含10%胎牛血清的DMEM培养基培养。miR-19模拟物（mimic）、miR-19抑制物（inhibitor）、PTEN过表达载体及阴性对照、qPCR试剂盒、BCA蛋白质分析试剂盒、ECL检测试剂盒、TRIzol®试剂盒均购自赛默飞世尔科技（中国）有限公司，Transwell小室购自美国康宁公司，一抗（抗PTEN抗体、抗p-Akt 308抗体、抗p-Akt 473抗体、抗Akt抗体和抗GAPDH抗体）与辣根过氧化物酶标记的山羊抗兔二抗均购自美国Abcam公司。

1.2　细胞分组与转染

将KLE细胞随机分为对照（NC）组、miR-19模拟物组和miR-19+PTEN组，待细胞生长至70%~90%汇合时，依照Lipofectamine™ 2000试剂说明书进行实验操作，向KLE细胞分别转染阴性对照片段（miR-NC）、miR-19模拟物或miR-19模拟物+PTEN过表达载体。转染48 h后，在荧光显微镜下观察细胞内荧光蛋白的表达情况以判断转染效率。

1.3　qPCR检测子宫内膜癌组织和细胞中miR-19和PTEN mRNA的表达水平

使用TRIzol试剂从各组细胞或组织中提取总RNA，采用试剂盒将提取的总RNA逆转录为cDNA，按照qPCR试剂盒说明书进行PCR反应，PCR反应条件为95 ℃预变性5 min，94 ℃变性30 s、60 ℃退火30 s，进行45个循环。miR-19的表达水平以U6为内参，PTEN mRNA的表达水平以GAPDH mRNA为内参，采用$2^{-\triangle\triangle Ct}$法计算相对表达量。

1.4　双荧光素酶报告基因实验验证miR-19与PTEN mRNA之间的靶向关系

通过TargetScan数据库预测miR-19在PTEN的3’-UTR上有潜在的结合位点，然后构建野生型PTEN 3’-UTR的荧光素酶报告基因质粒pMIR-WT-PTEN和携带突变型PTEN 3’-UTR的报告基因质粒pMIR-MUT-PTEN，将野生型或突变型报告基因质粒（以空载体pMIR为对照）与模拟物-NC、miR-19模拟物、抑制物-NC或miR-19抑制物共转染KLE细胞。转染24 h以后，利用双荧光素酶报告基因检测试剂盒检测各组细胞的荧光素酶活性。

1.5　WB法检测子宫内膜癌组织和细胞中PTEN、p-Akt 308和p-Akt 473蛋白的表达水平

用RIPA裂解缓冲液提取各组KLE细胞或子宫内膜癌组织的总蛋白，BCA法检测蛋白浓度，取上样缓冲液与样品混合并置于95 ℃变性10 min。蛋白样品以每孔20 μg上样，用10% SDS-PAGE分离蛋白，将蛋白转到PVDF膜上，用5%脱脂奶粉液封闭，2 h后加入抗PTEN抗体（1∶500）、抗p-Akt 308抗体（1∶500）、抗p-Akt 473抗体（1∶500）、抗Akt抗体（1∶500）和抗GAPDH抗体（1∶1 000），4 ℃摇床孵育过夜，弃未结合一抗并洗膜，加入辣根过氧化物酶标记的山羊抗兔二抗（1∶1 000）孵育1 h，洗膜后加入

ECL化学发光剂进行显色，暗室内显影。采用Quantity One凝胶分析软件采集照片并测定各组蛋白条带灰度值，以目的条带和GAPDH条带灰度值的比值作为目的蛋白的相对表达水平。

1.6 Transwell实验检测miR-19和PTEN对KLE细胞迁移和侵袭的影响

各组KLE细胞按1×10^{6}个/孔接种于Transwell上室，在下室加入完全培养液，24 h后取出小室，用无菌棉签轻拭去小室底部的聚碳酸酯膜上室内侧的细胞，PBS缓冲液冲洗膜3次，用95%乙醇固定10 min，结晶紫染色液染色，在显微镜下观察膜下室侧的迁移细胞并计数。Transwell侵袭实验中需预先用matrigel胶对Transwell小室进行预包被，其余步骤同迁移实验。

1.7 细胞划痕实验检测miR-19和PTEN对KLE细胞迁移的影响

将各组KLE细胞接种于6孔板上，当细胞汇合度达到80%~90%时，用200 μl的移液器吸头在正中央位置划一直线，形成单层细胞间的划痕，培养24 h，将细胞培养板置于显微镜下观察并拍照。用ImageJ软件测量迁移距离，计算各组细胞的划痕愈合率[划痕愈合率=(0 h宽度-24 h宽度)/0 h宽度×100%]。

1.8 统计学处理

采用SPSS Statistics 22.0软件进行分析，符合正态分布的计量数据用$\bar{x}\pm s$表示，两组数据间的比较采用t检验，3组或3组以上的比较采用One-way ANOVA，以P<0.05或P<0.01表示差异具有统计学意义。

2 结 果

2.1 PTEN在子宫内膜癌组织中呈低表达

采用qPCR（图1A）和WB法（图1B）检测PTEN mRNA和蛋白在子宫内膜癌组织和癌旁组织中的表达水平，结果显示，与癌旁组织相比，子宫内膜癌组织中PTEN mRNA表达明显降低（t=48.039，P<0.01），PTEN蛋白的表达也明显降低（0.37±0.03 *vs* 1.01±0.10，t=52.733，P<0.01）。

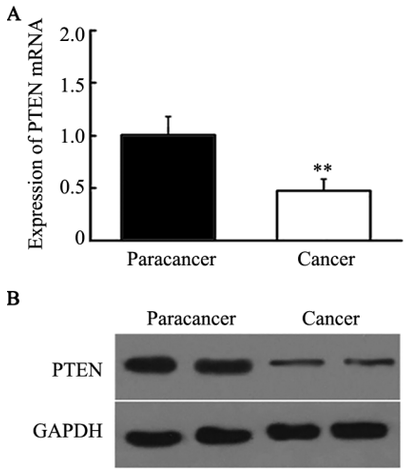
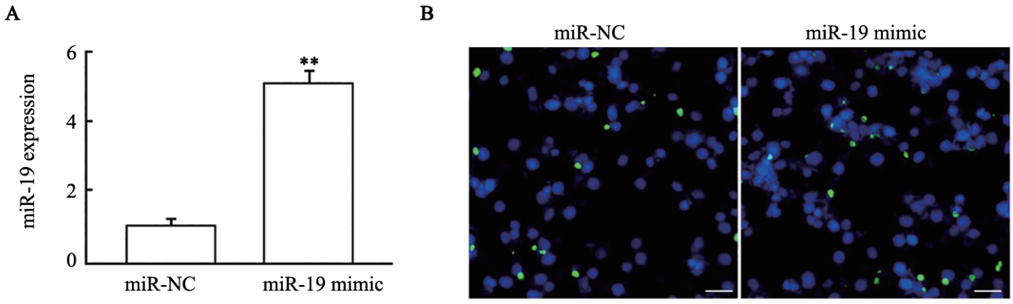


图1 PTEN mRNA（A）和蛋白（B）在子宫内膜癌组织中呈低表达

Fig. 1 PTEN was lowly expressed at both mRNA (A) and protein (B) level in endometrial cancer tissues

2.2 成功构建miR-19过表达的KLE细胞

将miR-19模拟物转染进KLE细胞中后，qPCR法检测结果（图2A）显示，miR-19摸拟物组KLE细胞中miR-19的表达明显高于对照组（t=14.648，P<0.01）；荧光显微镜下的观察结果（图2B）发现miR-19模拟物组阳性率（绿色）明显升高。



**P<0.01 *vs* miR-NC group

Blue: Nucleus were stained by DAPI; Green: GFP expressed by plasmids carrying miR-19 mimics

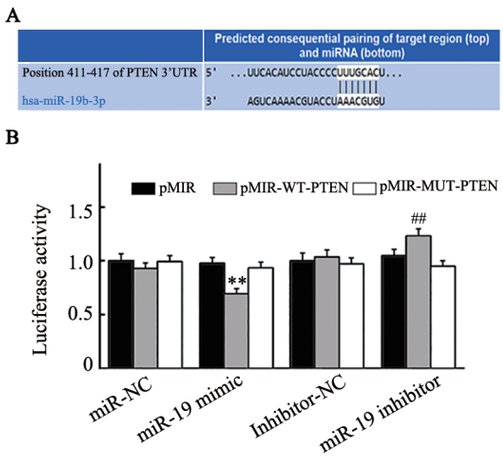
图2 qPCR法（A）和荧光显微镜观察（B）验证miR-19转染KLE细胞的效率（Scale bar=20 μm，×500）

Fig.2 The efficiency of miR-19 mimics transfecting KLE cells was verified by qPCR method (A) and fluorescence microscope observation (B) (Scale bar=20 μm, ×500)

2.3 PTEN是miR-19的潜在靶基因

采用TargetScan筛选miR-19的潜在靶基因，结果（图3A）显示，PTEN mRNA的3’-UTR上具有miR-19的潜在结合位点。双荧光素酶报告基因实验

结果（图3B）显示，与miR-NC组相比，miR-19模拟物+pMIR-WT-PTEN共转染组KLE细胞中荧光素酶活性明显降低（t=6.846，P<0.01），而miR-19模拟物+pMIR-MUT-PTEN共转染组细胞中荧光素酶活性无明显变化（P>0.05）。另一方面，与Inhibitor-NC组相比，miR-19抑制物+pMIR-WT-PTEN共转染组KLE细胞中荧光素酶活性显著升高（P<0.01），而miR-19抑制物+pMIR-MUT-PTEN组的荧光素酶活性无明显变化（P>0.05）。



$^{**}P$<0.01 *vs* miR-NC group; $^{\#\#}P$<0.01 *vs* Inhibitor-NC group

A: TargetScan software predicted that the 3'-UTR of PTEN mRNA has a binding site for miR-19; B: Dual luciferase reporter gene assay verified the targeting relationship between miR-19 and PTEN

图3　PTEN是miR-19的潜在靶基因

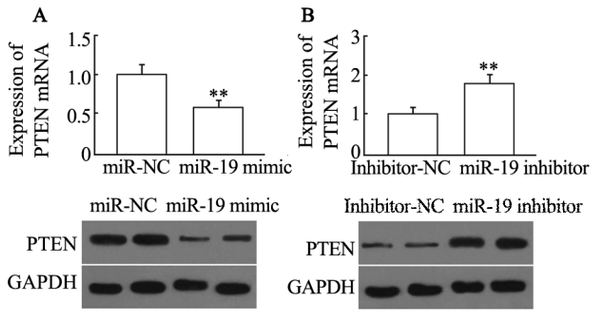
Fig.3　PTEN is a potential target gene of miR-19

2.4　miR-19负调控PTEN的表达

qPCR和WB法检测结果显示，miR-19模拟物组KLE细胞中PTEN mRNA（t=9.876，P<0.01）和蛋白（1.00±0.09 *vs* 0.36±0.03，t=11.685，P<0.01）的表达量明显低于miR-NC组（图4A），而miR-19抑制物组中PTEN mRNA（t=7.327，P<0.01）和蛋白（1.00±0.11 *vs* 1.87±0.19，t=6.864，P<0.01）的表达量较Inhibitor-NC组明显升高（图4B）。

2.5　miR-19和PTEN对KLE细胞迁移和侵袭的影响

Transwell实验和细胞划痕实验结果（图5）显示，miR-19模拟物组的迁移细胞数[（41.35±4.36）*vs*（26.34±2.71）个，F=28.16，P<0.01]和侵袭细胞数[（33.73±3.45）*vs*（21.71±2.26）个，F=46.30，P<0.01]均明显高于NC对照组，而miR-19+PTEN组的迁移细胞数[（22.51±2.31）个]和侵袭细胞数[（13.69±1.65）个]均较miR-19模拟物组明显降低（均P<0.01）；与NC对照组相比，miR-19模拟物组划痕愈合率显著增加[（0.54±0.11）% *vs*（0.05±0.01）%，P<0.01]，而与miR-19模拟物组相比，miR-19模拟物+PTEN组划痕愈合率显著降低[（0.32±0.07）% *vs*（0.54±0.11）%，P<0.01]。



$^{**}P$<0.01 *vs* miR-NC or Inhibitor-NC group

A : miR-19 mimics inhibited the mRNA and protein expression of PTEN; B: miR-19 inhibitors promoted the mRNA and protein expression of PTEN

图4　miR-19对PTEN mRNA和蛋白表达的调控

Fig.4　Regulation of miR-19 on the mRNA and protein expression of PTEN

2.6　miR-19通过靶向PTEN影响PI3K-Akt通路

WB法检测结果（图6）显示，与miR-NC组相比，miR-19模拟物组中PTEN蛋白的表达明显降低（P<0.01），而p-Akt 308和p-Akt 473蛋白的表达明显升高（均P<0.01），Akt蛋白的表达无明显变化；而在miR-19+PTEN组中，PTEN表达的上调部分逆转了miR-19的调控效果，p-Akt 308和p-Akt 473蛋白的表达均明显低于miR-19模拟物组（均P<0.01）。

3　讨　论

PTEN是重要的抑癌因子，其表达缺失与子宫内膜癌发生相关[13]。因此，探究PTEN在子宫内膜癌的表达对于了解其发病机制有重要意义。本研究发现，子宫内膜癌组织中PTEN的mRNA和蛋白表达均明显低于癌旁正常组织，亦提示PTEN与子宫内膜癌可能具有密切联系。

miRNA可通过调节靶基因的蛋白表达水平广泛参与各种生物过程和人类疾病[14-16]。本研究通过软件预测发现miR-19在PTEN的3'-UTR上具有潜在结合位点，并验证了PTEN的表达受miR-19的负性调控。miR-19已被证实与多种肿瘤相关，如在结直肠癌中抑制miR-19表达可以促进人结肠癌细胞HT29的凋亡，并抑制细胞的增殖、迁移和侵袭[17]；过表达miR-19可增强细胞增殖、侵袭和迁移，而抑制miR-19后细胞进展则受到抑制[18]。与以往研究结果类似，本研究发现上调miR-19能促进KLE细胞的迁移和侵袭，且这种影响会因PTEN表达的升高而被逆转，表明miR-19是通过靶向调控PTEN从而参与调

节子宫内膜癌细胞的生物学行为。PTEN能够通过抑制PI3K-Akt通路调控细胞周期、凋亡、迁移和侵袭等多种生物学过程，如miR-210通过PTEN/PI3K/Akt通路促进非小细胞肺癌细胞的迁移和侵袭[19]，miR-1179通过靶向PTEN介导的PI3K-Akt通路调控卵巢癌细胞的增殖[20]。为了进一步探究miR-19和PTEN在子宫内膜癌中的调控机制，本研究检测miR-19对PTEN相关信号通路的影响，结果发现，过表达miR-19后，KLE细胞中p-Akt 308和p-Akt 473蛋白的表达均明显升高，上调PTEN的表达能逆转这种影响，从而初步证实了miR-19可通过靶向调控PTEN从而影响PI3K-Akt通路，进而参与对子宫内膜癌的调节。

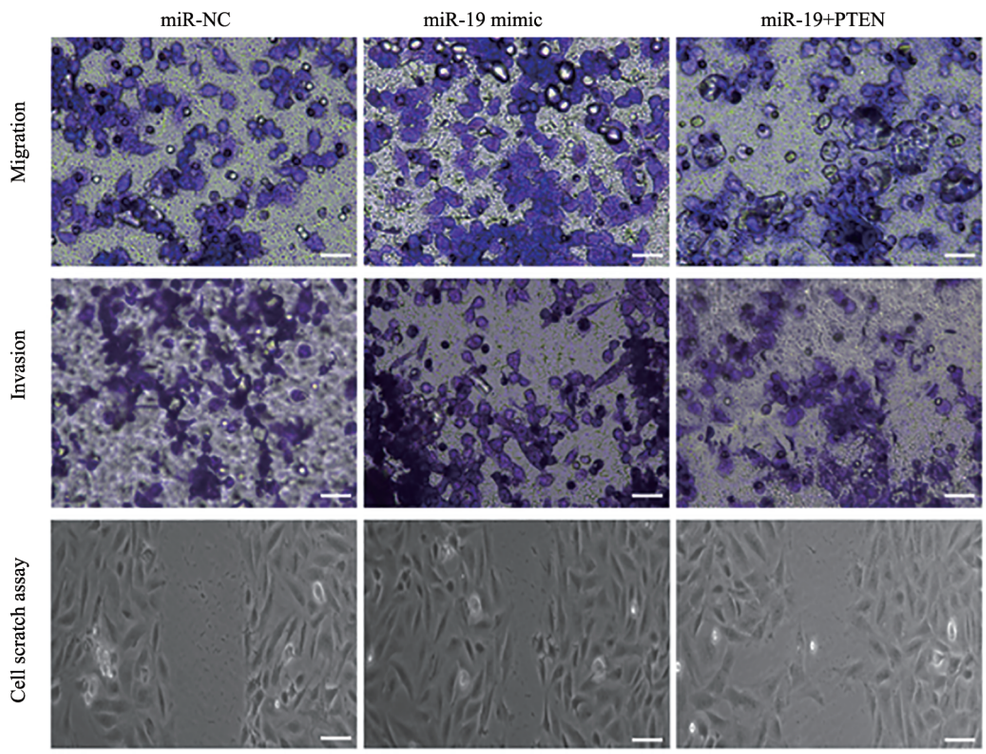
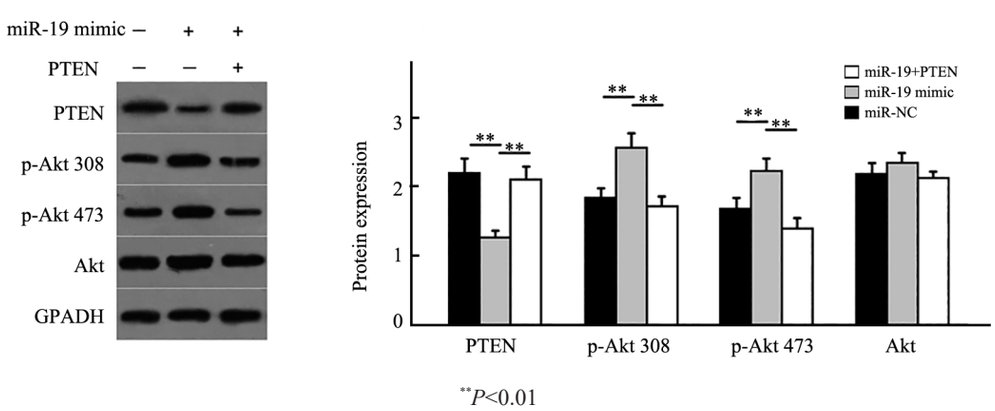


图5 Transwell和细胞划痕实验检测miR-19和PTEN对KLE细胞迁移和侵袭的影响（Scale bar=25 μm，×400）

Fig.5 The effects of miR-19 and PTEN on migration and invasion of KLE cells were detected by Transwell and cell scratch assay (Scale bar=25 μm, ×400)



$^{**}P<0.01$

图6 WB法检测miR-19对PI3K-Akt通路相关蛋白表达的影响

Fig.6 The effects of miR-19 on the expression of PI3K-Akt pathway related proteins were detected by WB

综上所述，本研究发现miR-19能通过靶向调控PTEN的表达活化PI3K-Akt通路，进而促进子宫内膜癌细胞KLE增殖、迁移等生物学行为，提示miR-19在子宫内膜癌中可能具有促癌因子的作用。在下一

步的研究中将深入探究miR-19与PTEN及其上游基因之间更复杂的相互作用。

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[收稿日期] 2021-07-27　　[修回日期] 2021-11-06
[本文编辑] 黄静怡