DOI:10.3872/j.issn.1007-385x.2018.09.007

·基础研究·

miR-195-5p靶向*FGF2*抑制子宫内膜癌HEC-1B细胞恶性生物学行为

李万斌[a],王新勇[b],周烨[b](济宁医学院a.临床学院;b.附属医院妇科,山东 济宁 272067)

[摘　要]　**目的:**探讨miR-195-5p通过靶向*FGF2*抑制子宫内膜癌HEC-1B细胞增殖、凋亡、侵袭和迁移的分子机制。**方法:**HEC-1B细胞培养与转染完成后分为4组:HEC-1B组、miR-195-5p mimic组、pLV-FGF2组和miR-195-5p+FGF2组。qRT-PCR检测细胞miR-195-5p和*FGF2* mRNA水平,荧光素酶实验验证miR-195-5p与FGF2的靶向关系,Western blotting检测FGF2表达水平,CCK-8法检测HEC-1B细胞增殖水平,流式细胞术检测HEC-1B细胞凋亡率,Transwell实验检测HEC-1B细胞侵袭能力,划痕实验检测HEC-1B细胞迁移能力。**结果:**与HEC-1B组相比,miR-195-5p mimic组miR-195-5p表达升高、*FGF2* mRNA水平下降(均P< 0.01);miR-195-5p可直接靶向*FGF2*。与HEC-1B组相比,miR-195-5p mimic组FGF2的蛋白表达 水平下降,pLV- FGF2组FGF2的蛋白水平明显上升,且miR-195-5p+FGF2组FGF2的蛋白表达水平低于pLV- FGF2组(均P< 0.01)。miR-195-5p mimic组细胞增殖水平低于HEC-1B组,pLV-FGF2组细胞增殖水平高于HEC-1B组(均P< 0.01)。与HEC-1B组相比,miR-195-5p mimic组细胞凋亡率增加,pLV- FGF2组细胞凋亡率降低,且miR-195-5p+ FGF2组细胞凋亡率高于pLV- FGF2组(均P< 0.01)。与HEC-1B组相比,miR-195-5p mimic组每个视野下的侵袭细胞数和划痕愈合率下降,pLV- FGF2组每个视野下的侵袭细胞数和划痕愈合率上升,且miR-195-5p+FGF2组每个视野下的侵袭细胞数和划痕愈合率低于pLV- FGF2组(均P<0.01)。**结论:** miR-195-5p通过靶向FGF2抑制子宫内膜癌HEC-1B细胞的增殖、侵袭和迁移并促进细胞凋亡,其作为子宫内膜癌的治疗靶点。

[关键词]　子宫内膜癌;HEC-1B细胞;miR-195-5p;增殖;凋亡;侵袭;迁移
[中图分类号]　R392.11; R737.33　[文献标识码]　A　[文章编号]　1007-385X(2018)09-0884-07

MiR-195-5p targeting *FGF2* inhibits malignant biological behaviors of endometrial carcinoma HEC-1B cells

LI Wanbin[a], WANG Xinyong[b], ZHOU Ye[b] (a. The Clinical College; b. Department of Gynecology, Affiliated Hospital of Jining Medical University, Jining 272067, Shandong, China)

[Abstract] Objective: To explore the molecular mechanism of miR-195-5p targeting *FGF2* to inhibit the proliferation, apoptosis, invasion and migration of endometrial cancer HEC-1B cells. **Methods:** After culture and transfection, HEC-1B cells were divided into 4 groups: HEC-1B group, miR-195-5p mimic group, pLV-FGF2 group and miR-195-5p+FGF2 group. The expressions of miR-195-5p and mRNA levels of FGF2 were detected by qRT-PCR. The targeted relationship of miR-195-5p and FGF2 was verified by luciferase assay. The protein expression of FGF2 was examined by Western blotting; Proliferation of HEC-1B cells was measured by CCK-8; Apoptosis was tested by flow cytometry; HEC-1B cell invasion was detected by transwell, and migration was measured by scratch assay. **Results:** Compared with HEC-1B group, the expression of miR-195-5p in miR-195-5p mimic group was elevated while FGF2 mRNA level was declined (all P<0.01). Luciferase assay indicated that FGF2 was a target of miR-195-5p. Compared with HEC-1B group, the protein level of FGF2 in miR-195-5p mimic group was decreased, and the protein levels of FGF2 in pLV-FGF2 group were enhanced (P<0.01). The protein levels of FGF2 in miR-195-5p+FGF2 group were lower than that in pLV-FGF2 group (all P<0.01). The proliferation in miR-195-5p mimic group was lower than HEC-1B group (P<0.01), while the proliferation in pLV-FGF2 group was higher than that in HEC-1B group (all P<0.01). Compared with HEC-1B group, apoptosis in miR-195-5p mimic group was increased, and apoptosis in pLV-FGF2 group was decreased (P<0.01); moreover, apoptosis in miR-195-5p+FGF2 group was higher than that in pLV-FGF2 group (P<0.01). Compared with HEC-1B group, the number of invasive cells per field and the rate of wound healing in miR-195-5p mimic group were decreased, while those in pLV-FGF2 group was enhanced (P<0.01); moreover, the number of invasive cells per field and the rate of wound healing in miR-195-5p+FGF2 group was lower than those in pLV-FGF2 group (all P<0.01). **Conclusion:** miR-195-5p inhibits proliferation, invasion and migration and promotes apoptosis of endometrial cancer HEC-1B cells by target-

[基金项目]　山东省自然科学基金资助项目(No.Q98C01124)。Project supported by the Natural Science Foundation of Shandong Province (No. Q98C01124)
[作者简介]　李万斌(1974-),女,硕士,讲师,主要从事妇科肿瘤的基础与临床研究,E-mail:chenwangkzsdr@163.com

ing FGF2, and could be used as a treatment target of endometrial cancer.

[Key words] endometrial cancer; HEC-1B cell; miR-195-5p; proliferation; apoptosis; invasion; migration

[Chin J Cancer Biother, 2018, 25(9): 884-890. DOI：10.3872/j.issn.1007-385X.2018.09.007]

子宫内膜癌是世界上第六大常见癌症，也是继宫颈癌之后的全球第二大妇科癌症，每年约有7.4万名女性死于宫内膜癌[1-3]。MicroRNAs是一类长度约为22个核苷酸的非编码RNA，涉及基因转录后调控，在细胞生物学过程中起着重要作用。研究[4]表明，microRNAs的异常表达与包括癌症在内的各种疾病密切相关，其在癌症的发生发展进程及抗药性方面发挥着重要作用。大量数据[5-6]显示，子宫内膜癌中存在着大量异常表达的microRNAs，这些microRNAs与细胞增殖、凋亡、侵袭和转移存在密切联系。有研究[7-10]显示，miR-195-5p在子宫内膜癌中低表达，在前列腺癌、甲状腺癌及膀胱癌等癌症发挥着重要的调控作用。本研究旨在观察miR-195-5p通过靶向FGF2对子宫内膜癌HEC-1B细胞增殖、凋亡、侵袭和迁移的影响及其分子作用机制，为子宫内膜癌的靶向治疗提供实验基础。

1 材料与方法

1.1 细胞系及主要试剂

子宫内膜癌细胞系HEC-1B购自美国典型培养物保藏中心(American Type Culture Collection, ATCC)。DMEM培养基、胎牛血清及转染试剂turbo-Fect transfection regent购自赛默飞世尔科技公司，增强miR-195-5p表达的特异性序列miR-195-5p mimic及其阴性对照非特异性序列NC、FGF2慢病毒表达载体pLV- FGF2以及含野生型和突变型FGF2序列的荧光素酶报告基因质粒由上海吉玛制药技术有限公司提供，总RNA提取试剂盒TRIzol reagent及其反转录试剂盒PrimeScript® RT reagent Kit、microRNA提取试剂盒RNAiso for Small RNA及其反转录试剂盒One Step PrimeScript® miRNA cDNA Synthesis Kit和定量PCR试剂盒SYBR Premix Ex Taq™购自大连TaKaRa公司，荧光素酶检测试剂盒来源于Promega公司，Annexin V-FITC/PI细胞凋亡检测试剂盒购自Solarbio公司，Transwell小室及人工基底膜购自美国BD公司，抗成纤维细胞生长因子2 (fibroblast growth factor 2, FGF2)抗体购自英国Abcam公司。

1.2 细胞培养与转染

HEC-1B细胞于含10%胎牛血清和1%青-链霉素的DMEM培养基中，并置于37 ℃、5% CO_2的恒温培养箱中培养。当细胞汇合度70%~80%时进行传代。HEC-1B细胞分为4组：HEC-1B组、miR-195-5p mimic组、pLV- FGF2组和miR-195-5p+ FGF2组。为了提高miR-195-5p和FGF2表达，按照转染试剂turbofect transfection regent说明书将miR-195-5p mimic (5’- UAGCAGCACAGAAAUAUUGGC -3’)及pLV-FGF2分别转入HEC-1B细胞中。

1.3 qRT-PCR检测miR-195-5p和*FGF2* mRNA表达水平

细胞转染前及转染mimic-NC、miR-195-5p mimic后检测miR-195-5p和*FGF2*mRNA表达水平。运用RNA提取试剂盒提取RNA后进行反转录。根据SYBR Premix Ex Taq™说明书进行qRT-PCR，其引物序列如下：miR-195-5p上游引物为5’-GATAGCAGCACAGAAATATTGGC-3’，下游引物为5’-CAGTGCGTGTCGTGGAGT-3’；*FGF2*上游引物为5’-AGAAGAGCGACCCTCACATCA-3’、下游引物为5’- CGGTTAGCACACACTCCTTTG-3’。用公式$2^{-\Delta\Delta Ct}$计算miR-195-5p和*FGF2* mRNA表达水平。实验重复3次。

1.4 荧光素酶实验验证miR-195-5p与FGF2的靶向作用关系

按照转染试剂turbofect transfection regent说明书将FGF2野生型或突变型的荧光素酶报告基因质粒载体单独转入细胞中，或同时添加miR-138 mimic转入细胞，培养48 h后移去培养液。加入PBS洗涤细胞，弃去洗涤液，在孔中加入细胞裂解液将细胞裂解。室温下振荡器上振荡5~10 min，移入离心管中3 000×*g*离心5 min，取上清进行发光测定。按照试剂盒说明书和仪器操作说明对待测样品进行发光值测定。实验重复3次。

1.5 Western blotting检测转染前后HEC-1B细胞中FGF2的表达

用PBS将待测细胞清洗3次，加入含蛋白酶抑制剂的细胞裂解液提取总蛋白，100 ℃变性5 min。等量蛋白进行SDS-PAGE分离并转至PVDF膜。经5%的BSA封闭1 h后加入抗FGF2的一抗，4 ℃过夜孵育。再加入辣根过氧化物酶标记的二抗，室温孵育1.5 h。加入发光液后于凝胶成像仪进行曝光拍照，并统计灰度值计算相对表达量。实验重复3次。

1.6 CCK-8法检测HEC-1B细胞增殖率

首先将各组待测细胞用稀释到10%的CCK-8溶液制成1×10^6个/ml的细胞悬液，然后在37 ℃恒温培养箱中培养4 h，最后检测450 nm处光密度(*D*)值，计算细胞增殖倍数，绘制生长曲线。实验重复3次。

1.7　流式细胞术检测HEC-1B细胞凋亡率

收集各组待测细胞，经PBS洗涤后用Binding buffer将细胞制成1×10^6个/ml的悬液。然后加入Annexin V-FITC，混匀，室温下避光孵育10 min。再加入PI，室温下避光孵育5 min，流式细胞仪对染色的细胞进行检测。实验重复3次。

1.8　Transwell实验检测HEC-1B细胞侵袭能力

首先各组待测细胞悬浮于无胎牛血清的DMEM培养基中，细胞密度为1×10^6个/ml。然后在Transwell的下室中加入含20%胎牛血清的DMEM培养基，在铺有人工基底膜的Transwell的上室中加入上述细胞悬液。37 ℃培养24 h后，用0.5%的结晶紫对上室底部细胞进行染色，并用棉签除去上室内侧的细胞，显微镜下观察并统计细胞数量。

1.9　划痕实验检测HEC-1B细胞细胞迁移能力

将各组待测细胞制成细胞密度为1×10^6个/ml的细胞悬液加入到6孔板中，过夜培养至形成单层细胞。在单层细胞上用10 μl的枪头划横线，用PBS洗去因划线而脱落的细胞，显微镜下拍照记录划痕宽度，继续培养24 h后，显微镜下拍照记录划痕宽度，计算划痕愈合率(%)=(初始划痕宽度-培养24 h后划痕宽度)/初始划痕宽度×100%。

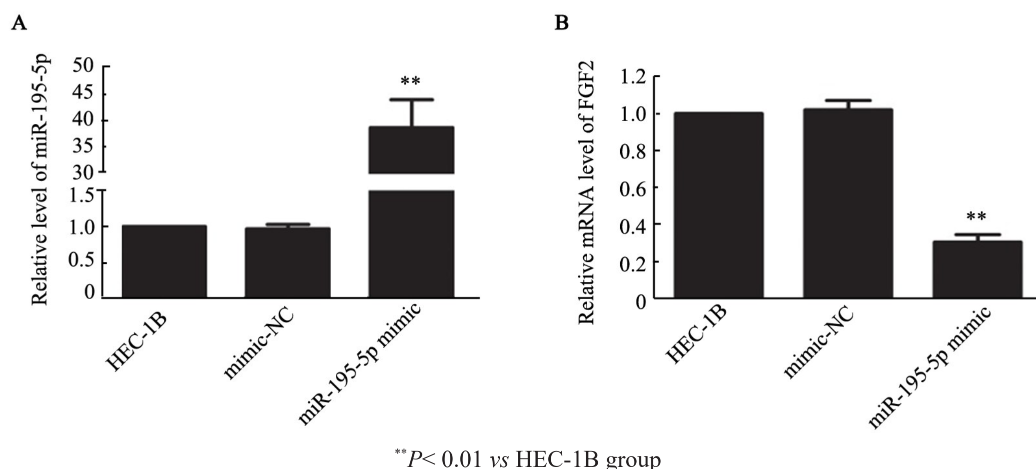
1.10　统计学处理

采用SPSS 25.0统计学软件和GraphPad Prism 5.0作图软件，数据以$\bar{x}\pm s$表示，两组间比较采用t检验；多组间比较采用单因素方差分析。以$P<0.05$或$P<0.01$表示差异有统计学意义。

2　结　果

2.1　转染miR-195-5p mimic可提高或降低HEC-1B细胞miR-195-5p和*FGF2* mRNA表达水平

qRT-PCR检测结果（图1）显示，子宫内膜癌HEC-1B细胞转染miR-195-5p mimic后miR-195-5p mimic组miR-195-5p表达明显高于HEC-1B组，*FGF2* mRNA水平低于HEC-1B组(均$P<0.01$)。



$^{**}P<0.01$ *vs* HEC-1B group

图1 转染miR-195-5p mimic对HEC-1B细胞miR-195-5p（A）和*FGF2* mRNA（B）表达水平的影响

Fig. 1 Effect of miR-195-5p mimic transfection on the mRNA expressions of miR-195-5p（A）and *FGF2*（B）

2.2　miR-195-5p直接靶向作用于*FGF2*

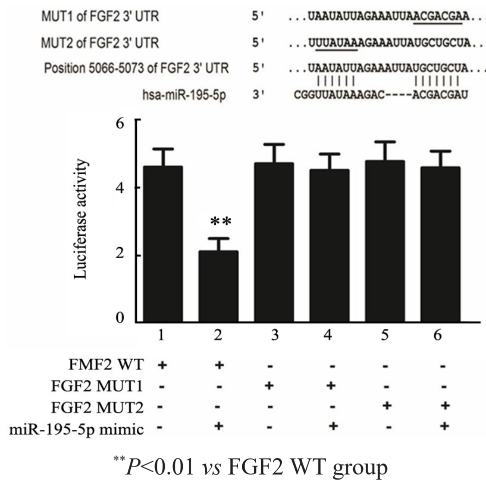
荧光素酶实验进一步验证结果（图2）显示，转染野生型和突变型*FGF2*序列质粒的细胞中荧光素酶活性无明显差异（$P>0.05$）；转染miR-195-5p mimic和野生型FGF2序列质粒与单独转染野生型*FGF2*序列质粒比较，荧光素酶活性明显下降($P<0.01$)；转染miR-195-5p mimic和突变型*FGF2*序列质粒与单独转染突变型*FGF2*序列质粒相比，荧光素酶活性无明显变化（$P>0.05$）。上述结果表明miR-195-5p直接靶向作用于*FGF2*。

2.3　miR-195-5p负向调控HEC-1B细胞FGF2蛋白的表达水平

Western blotting实验检测结果（图3）显示，与HEC-1B组相比，miR-195-5p mimic组FGF2的蛋白表达水平下降，pLV-FGF2组的FGF2蛋白水平上升，miR-195-5p+FGF2组FGF2的蛋白水平低于pLV-FGF2组(均$P<0.01$)，表明miR-195-5p负向调控FGF2表达。

2.4　miR-195-5p靶向FGF2明显降低HEC-1B细胞增殖水平

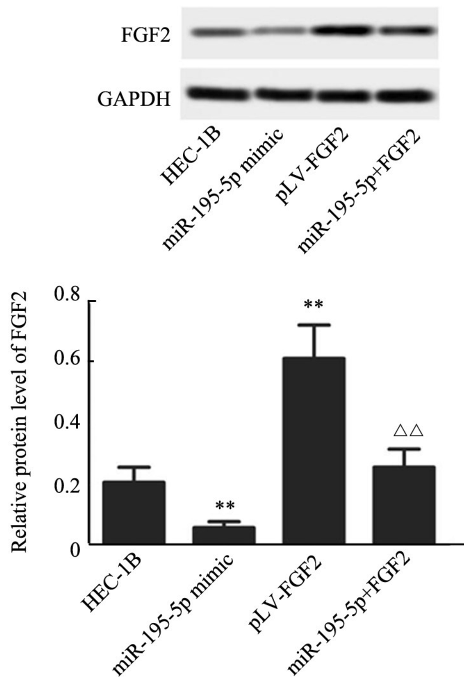
CCK-8法检测结果（图4）显示，与HEC-1B组相比，miR-195-5p mimic组细胞增殖率较HEC-1B组明显降低，pLV-FGF2组细胞增殖水平升高，且miR-195-5p+FGF2组细胞增殖水平低于pLV-FGF2组(均$P<0.01$)，表明miR-195-5p靶向FGF2可降低子宫内膜癌HEC-1B细胞增殖水平。



$^{**}P$<0.01 *vs* FGF2 WT group

图2 miR-195-5p与FGF2的靶向关系

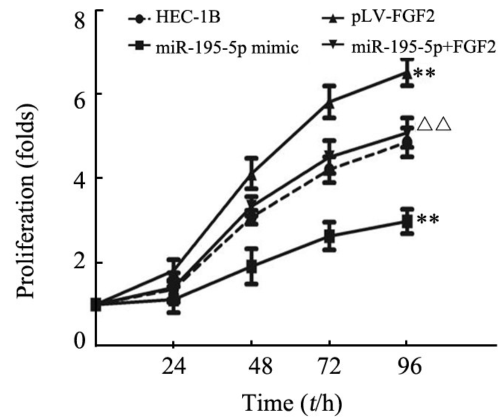
Fig. 2 Target relationship between miR-195-5p and FGF2



$^{**}P$<0.01 *vs* HEC-1B group, $^{\triangle\triangle}P$<0.01 *vs* pLV-FGF2 group

图3 miR-195-5p对HEC-1B细胞FGF2蛋白表达水平影响

Fig. 3 Effect of miR-195-5p on the expression level of FGF2 protein in HEC-1B cells



$^{**}P$<0.01 *vs* HEC-1B group, $^{\triangle\triangle}P$<0.01 *vs* pLV-FGF2 group

图4 miR-195-5p靶向FGF2对HEC-1B细胞增殖率的影响

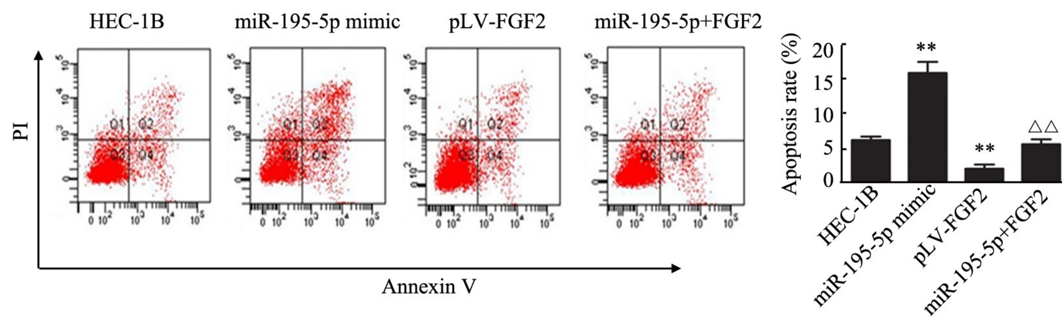
Fig. 4 Effect of miR-195-5p targeting FGF2 on proliferation of HEC-1B cells

2.5 miR-195-5p靶向FGF2明显促进HEC-1B细胞凋亡

流式细胞术检测结果(图5)显示,与HEC-1B组相比,miR-195-5p mimic组HEC-1B细胞凋亡率明显增加,pLV-FGF2组HEC-1B细胞凋亡率明显降低,且miR-195-5p+FGF2组细胞凋亡率明显高于pLV-FGF2组(均*P*< 0.01)。表明miR-195-5p靶向FGF2可促进子宫内膜癌HEC-1B细胞凋亡。

2.6 miR-195-5p靶向FGF2可降低HEC-1B细胞侵袭能力

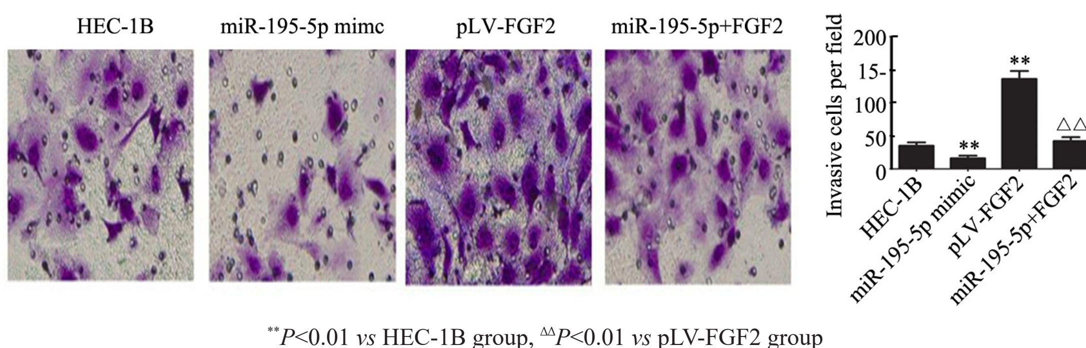
Transwell实验检测结果(图6可知,与HEC-1B组相比,miR-195-5p mimic组每个视野下的侵袭细胞数明显下降,pLV-FGF2组每个视野下的侵袭细胞数明显上升,且miR-195-5p+FGF2组每个视野下的侵袭细胞数明显少于pLV-FGF2组(均*P*<0.01)。表明miR-195-5p靶向FGF2可降低子宫内膜癌HEC-1B细胞侵袭能力。



$^{**}P$<0.01 *vs* HEC-1B group, $^{\triangle\triangle}P$<0.01 *vs* pLV-FGF2 group

图5 miR-195-5p靶向FGF2对HEC-1B细胞凋亡的影响

Fig. 5 Effect of miR-195-5p targeting FGF2 on the apoptosis of HEC-1B cells



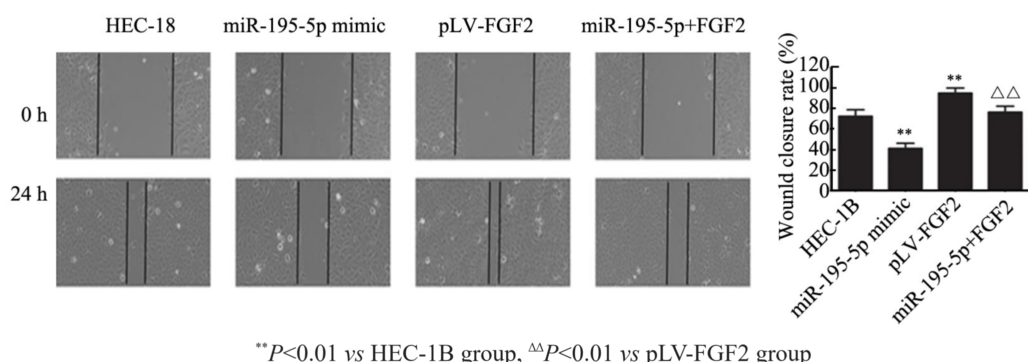
$^{**}P$<0.01 *vs* HEC-1B group, $^{\triangle\triangle}P$<0.01 *vs* pLV-FGF2 group

图6　miR-195-5p靶向FGF2对HEC-1B细胞侵袭能力的影响(×200)

Fig. 6　Effect of miR-195-5p targeting FGF2 on invasion ability of HEC-1B cells(×200)

2.7　miR-195-5p靶向FGF2对子宫内膜癌HEC-1B细胞迁移的影响

为分析miR-195-5p靶向FGF2对子宫内膜癌HEC-1B细胞迁移的影响，利用划痕实验检测细胞迁移。图7显示，与HEC-1B组相比，miR-195-5p mimic组划痕愈合率降低，pLV-FGF2组划痕愈合率上升(*P* < 0.01)。miR-195-5p+FGF2组划痕愈合率低于pLV-FGF2组(*P*< 0.01)。上述结果表明，miR-195-5p靶向FGF2可减弱子宫内膜癌HEC-1B细胞迁移。



$^{**}P$<0.01 *vs* HEC-1B group, $^{\triangle\triangle}P$<0.01 *vs* pLV-FGF2 group

图7　miR-195-5p靶向FGF2对子宫内膜癌HEC-1B细胞迁移的影响

Fig. 7　Effect of miR-195-5p targeting FGF2 on migration of endometrial carcinoma HEC-1B cells

3　讨　论

目前对早期子宫内膜癌的治疗方法主要是手术切除，但手术治疗存在各种副作用包括不孕、、停经、下肢淋巴水肿及性功能障碍，严重影响患者的生活质量[11-12]。对于转移性和复发性子宫内膜癌则无法采用手术切除，需要进行药物治疗。但目前的抗肿瘤药物存在比较大的毒副作用。随着分子生物学的发展，分子靶向治疗受到了越来越多的关注，其中microRNAs具有成为治疗靶点的潜能[13-15]。

细胞增殖不受控是癌细胞的常见特征，大量数据表明miR-195-5p可调节癌细胞增殖。ZHANG等[16]研究发现，miR-195-5p可靶向HMGA1降低前列腺癌细胞增殖能力。也有研究[17-19]表明，在乳腺癌细胞中miR-195-5p可通过调节IRS1抑制细胞增殖；在宫颈癌细胞中miR-195-5p可直接靶向cyclin D1减弱细胞增殖；miR-195-5p也可通过靶向FGF2抑制结肠直肠癌细胞增殖。本研究结果显示，在子宫内膜癌HEC-1B细胞中添加miR-195-5p mimic会降低细胞增殖率，且会逆转pLV-FGF2对细胞增殖的促进作用，这说明miR-195-5p可通过靶向FGF2减弱子宫内膜癌HEC-1B细胞增殖。

癌细胞具有抗细胞凋亡的特点，而miR-195-5p具有促进癌细胞凋亡的功能。有数据[20]显示，miR-195-5p可靶向GLUT3促进膀胱癌细胞凋亡。CHEN等[21]研究发现，在肾脏上皮肾细胞癌中miR-195-5p可直接靶向REGγ，增强细胞凋亡。也有研究[22]表明，miR-195-5p靶向TRIM14，促进口腔鳞状细胞癌细胞凋亡。本研究结果显示，在子宫内膜癌HEC-1B细胞中添加miR-195-5p mimic会提高细胞凋亡率，且会减弱pLV-FGF2对细胞凋亡的抑制作用，这表明miR-195-5p可通过靶向FGF2促进子宫内膜癌HEC-1B细胞凋亡。

细胞侵袭能力在癌症转移中起着重要作用，大

量研究表明miR-195-5p可调控癌细胞的侵袭能力。有研究[23]显示，在骨肉瘤细胞中，miR-195-5p可负向调控NKD1表达，降低细胞侵袭。LUO等[24]研究发现，在结肠癌细胞中miR-195-5p可直接靶向CDK8，抑制细胞侵袭。研究[25]显示，miR-195-5p可负向调控前列腺癌细胞Fra1表达，减弱细胞侵袭。也有研究[26]发现，miR-195-5p可通过靶向FGF2抑制肝癌细胞侵袭。本研究结果显示，在子宫内膜癌HEC-1B细胞中添加miR-195-5p mimic会减弱细胞侵袭，且会抑制pLV-FGF2对细胞侵袭的促进作用，这说明miR-195-5p可通过靶向FGF2降低子宫内膜癌HEC-1B细胞侵袭。

细胞迁移对癌症进程的发展十分重要，miR-195-5p具有调节癌细胞迁移的功能。GUO等[27]研究发现，miR-195-5p可靶向HDGF减弱非小细胞肺癌细胞迁移。miR-195-5p也可靶向结肠直肠癌细胞YAP1，降低细胞迁移[28]。有研究[29]显示，miR-195-5p靶向Notch2可减弱骨肉瘤细胞迁移。也有数据[30]显示，miR-195-5p可通过靶向FGF2抑制前列腺癌细胞迁移。本研究结果显示，在子宫内膜癌HEC-1B细胞中添加miR-195-5p mimic会减弱细胞迁移，且会抑制pLV-FGF2对细胞迁移的促进作用，这表明miR-195-5p可通过靶向FGF2降低子宫内膜癌HEC-1B细胞迁移。

综上所述，在子宫内膜癌HEC-1B细胞中，miR-195-5p可直接靶向作用FGF2，负向调控其表达，减弱癌细胞增殖、侵袭和迁移，并促进细胞凋亡，从而发挥抗癌作用，为子宫内膜癌的治疗提供新的靶点。

[参 考 文 献]

[1] SHAW E, FARRIS M, MCNEIL J, et al. Obesity and endometrialcancer[J]. Recent Results Cancer Res, 2016,208（2）: 107-136. DOI: 10.1007/978-3-319-42542-9_7.

[2] BINDER P S, MUTCH D G. Update on prognostic markers for endometrial cancer[J]. Womens Health (Lond), 2014, 10(3): 277-288. DOI:10.2217/whe.14.13.

[3] BELL D W. Novel genetic targets in endometrial cancer[J]. Expert Opin Ther Targets, 2014, 18(7): 725-730. DOI: 10.1517/14728222.2014.909414.

[4] ACUNZO M, ROMANO G, WERNICKE D, et al. MicroRNA and cancer--a brief overview[J]. Adv Biol Regul, 2015,57（1）: 1-9. DOI: 10.1016/j.jbior.2014.09.013.

[5] VASILATOU D, SIOULAS V D, PAPPA V, et al. The role of miRNAs in endometrial cancer[J]. Epigenomics, 2015, 7(6): 951-959. DOI:10.2217/epi.15.41.

[6] YANOKURA M, BANNO K, IIDA M, et al. Micrornas in endometrial cancer: Recent advances and potential clinical applications [J]. Excli J, 2015,14(5): 190-198. DOI: 10.17179/excli2014-590.

[7] JAYARAMAN M, RADHAKRISHNAN R, MATHEWS C A, et al. Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer[J]. Genes Cancer, 2017, 8(5/6): 566-576. DOI: 10.18632/genesandcancer.144.

[8] CAI C, CHEN Q B, HAN Z D, et al. miR-195inhibitstumorprogression by targetingrps6kb1 in humanprostatecancer[J]. Clin Cancer Res, 2015, 21(21): 4922-4934. DOI: 10.1158/1078-0432. CCR-15-0217.

[9] WANG F, JIANG C, SUN Q, et al. MiR-195 is a key regulator of Raf1 in thyroid cancer[J/OL]. Onco Targets Ther, 2015, 8: 3021-3028[2018-04-06]. https://www. ncbi. nlm. nih. gov / pmc / articles / PMC4621222/. DOI:10.2147/OTT.S90710.

[10] ZHAO C, QI L, CHEN M, et al. MicroRNA-195 inhibits cell proliferation in bladder cancer via inhibition of cell division control protein 42 homolog/signal transducer and activator of transcription-3 signaling[J]. Exp Ther Med, 2015, 10(3): 1103-1108. DOI:10.3892/etm.2015.2633.

[11] CONWAY J L, LUKOVIC J, LAFRAMBOISE S, et al. Brachy-ing unresectableendometrialcancers with magneticresonanceguidance[J/OL]. Cureus, 2018, 10(3): e2274[2018-04-06]. https://www. ncbi. nlm.nih.gov/pmc/articles/PMC5935429/.DOI:10.7759/cureus.2274.

[12] 顾星, 曹方, 胡永伟, 等. 小脑锌指结构1基因在人子宫内膜癌中的表达及其预后预测价值[J]. 中国肿瘤生物治疗杂志, 2017, 24(8)：875-879.DOI：10.3872/j.issn.1007-385X.2017.08.010.

[13] SILVA J L, PAULINO E, DIAS M F, et al. Endometrial cancer: redefining the molecular-targeted approach[J]. Cancer Chem Pharmacol, 2015,76(1):1-11. DOI:10.1007/s00280-015-2758-z.

[14] LHEUREUX S, OZA A M. Endometrial cancer-targeted therapies myth or reality? Review of current targeted treatments[J]. Eur J Cancer, 2016, 59(2): 99-108. DOI:10.1016/j.ejca.2016.02.016.

[15] HAYES J, PERUZZI P P, LAWLER S. MicroRNAs in cancer: biomarkers, functions and therapy[J]. Trends Mol Med, 2014, 20(8): 460-469. DOI:10.1016/j.molmed.2014.06.005.

[16] ZHANG X, TAO T, LIU C, et al. Downregulation of miR-195 promotes prostate cancer progression by targeting HMGA1[J]. OncolRep, 2016, 36(1): 376-382. DOI:10.3892/or.2016.4797.

[17] WANG Y, ZHANG X, ZOU C, et al. miR-195 inhibits tumor growth and angiogenesis through modulating IRS1 in breast cancer [J]. Biomed Pharmacother, 2016, 80（2）: 95-101. DOI:10.1016/j.biopha.2016.03.007.

[18] LI Z, WANG H, WANG Z, et al. MiR-195 inhibits the proliferation of human cervical cancer cells by directly targeting cyclin D1[J]. Tumour Biol, 2016, 37(5): 6457-6463. DOI: 10.1007/s13277-015-4540-6.

[19] ZHANG X, XU J, JIANG T, et al. MicroRNA-195 suppresses colorectal cancer cells proliferation via targeting FGF2 and regulating Wnt/β-catenin pathway[J]. Am J Cancer Res, 2016,6(11):2631-2640.

[20] FEI X, QI M, WU B, et al. MicroRNA-195-5p suppresses glucose uptake and proliferation of human bladder cancer T24 cells by regulating GLUT3 expression[J]. FEBS Lett, 2012, 586(4): 392-397. DOI:10.1016/j.febslet.2012.01.006.

[21] CHEN S, WANG L, YAO X, et al. miR-195-5p is critical in REGγ-mediated regulation of wnt/β-catenin pathway in renal cell carcinoma[J]. Oncotarget, 2017, 8(38): 63986-64000. DOI:10.18632/oncotarget.19256.

[22] WANG T, REN Y, LIU R, et al. miR-195-5psuppresses the proliferation, migration, and invasion of oralsquamouscellcarcinoma by targetingTRIM14[J/OL]. Biomed Res Int, 2017, 2017: 7378148[2018-04-06]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674489/. DOI: 10.1155/2017/7378148.

[23] QU Q, CHU X, WANG P. MicroRNA-195-5p suppresses osteosarcoma cell proliferation and invasion by suppressing naked cuticle homolog 1[J]. Cell Biol Int, 2017, 41(3): 287-295. DOI: 10.1002/cbin.10723.

[24] LUO Q, ZHANG Z, DAI Z, et al. Tumor-suppressive microRNA-195-5p regulates cell growth and inhibits cell cycle by targeting cyclin dependent kinase 8 in colon cancer[J]. Am J Transl Res, 2016, 8(5): 2088-2096.

[25] WU J, JI A, WANG X, et al. MicroRNA-195-5p, a new regulator of Fra-1, suppresses the migration and invasion of prostate cancer cells[J]. J Transl Med, 2015,13(4): 289-294. DOI:10.1186/s12967-015-0650-6.

[26] WANG M, ZHANG J, TONG L, et al. MiR-195 is a key negative regulator of hepatocellular carcinoma metastasis by targeting FGF2 and VEGFA[J]. Int J Clin Exp Pathol, 2015, 8(11): 14110-14120.

[27] GUO H, LI W, ZHENG T, et al. MiR-195 targets HDGF to inhibit proliferation and invasion of NSCLC cells[J]. Tumour Biol, 2014,35(9): 8861-8866. DOI:10.1007/s13277-014-2153-0.

[28] SUN M, SONG H, WANG S, et al. Integrated analysis identifies microRNA-195 as a suppressor of Hippo-YAP pathway in colorectal cancer[J]. J Hematol Oncol, 2017, 10(1): 79-86. DOI: 10.1186/s13045-017-0445-8.

[29] ZHOU S, YU L, XIONG M, et al. LncRNASNHG12 promotes tumorigenesis and metastasis in osteosarcoma by upregulating Notch2 by sponging miR-195-5p[J]. Biochem Biophys Res Commun, 2018, 495(2): 1822-1832. DOI:10.1016/j.bbrc.2017.12.047.

[30] LIU C, GUAN H, WANG Y, et al. Mir-195 inhibits emt by targeting FGF2 in prostate cancer cells[J / OL]. PLoS One, 2015, 10(12): e0144073[2018-04-06].https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4674136/.DOI: 10.1371/journal.pone.0144073.

[收稿日期]　2018-05-10　　[修回日期]　2018-07-21
[本文编辑]　王映红