

## 论 著

# miR-1285对卵巢癌OVCAR3细胞侵袭迁移的影响及其机制

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**[摘要]** 目的 探讨微小RNA(miR)-1285对卵巢癌OVCAR3细胞侵袭、迁移的影响及其作用机制。方法 取对数生长期人卵巢癌OVCAR3细胞, 随机分为对照组(仅加入脂质体)、miR-1285-NC组(转染随机无义序列)、miR-1285-mimics组(转染miR-1285拟似物)、miR-1285-mimics+Yes相关蛋白1(YAP1)组(转染miR-1285拟似物及YAP1过表达序列)。取稳定转染的各组细胞, qRT-PCR法检测miR-1285相对表达水平, 划痕实验检测细胞迁移能力, Transwell实验检测细胞侵袭能力, Western blotting法检测细胞中YAP1、E-钙黏蛋白(E-cadherin)及波形蛋白的相对表达水平。结果 与对照组、miR-1285-NC组比较, miR-1285-mimics组、miR-1285-mimics+YAP1组miR-1285相对表达水平均明显升高, 差异有统计学意义( $P<0.05$ ); 对照组与miR-1285-NC组、miR-1285-mimics组与miR-1285-mimics+YAP1组比较miR-1285相对表达水平差异无统计学意义( $P>0.05$ )。与对照组、miR-1285-NC组比较, miR-1285-mimics组、miR-1285-mimics+YAP1组划痕愈合率降低, 穿膜细胞数减少, 差异有统计学意义( $P<0.05$ ); 其中miR-1285-mimics+YAP1组划痕愈合率明显高于miR-1285-mimics组, 且穿膜细胞数明显多于miR-1285-mimics组( $P<0.05$ )。与对照组、miR-1285-NC组比较, miR-1285-mimics组、miR-1285-mimics+YAP1组YAP1、波形蛋白相对表达水平降低, E-cadherin蛋白相对表达水平升高, 差异有统计学意义( $P<0.05$ ); miR-1285-mimics+YAP1组YAP1、波形蛋白相对表达水平明显高于miR-1285-mimics组, E-cadherin蛋白相对表达水平明显低于miR-1285-mimics组, 差异有统计学意义( $P<0.05$ )。miR-1285-NC组划痕愈合率、穿膜细胞数及YAP1、E-cadherin、波形蛋白相对表达水平与对照组比较差异均无统计学意义( $P>0.05$ )。结论 过表达miR-1285可能通过下调YAP1表达而发挥抑制卵巢癌细胞侵袭及迁移的作用。

**[关键词]** 卵巢癌; 微小RNA-1285; Yes相关蛋白1; 细胞侵袭; 细胞迁移

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## Effect of miR-1285 on the invasion and migration of ovarian cancer OVCAR3 cells and its mechanism

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**[Abstract]** **Objective** To investigate the effect of miR-1285 on migration and invasion of ovarian cancer OVCAR3 cells and its mechanism. **Methods** Human ovarian cancer OVCAR3 cells in logarithmic growth phase were collected and randomly divided into control group (liposomes added only), miR-1285-NC group (transfected randomly, nonsense sequence), miR-1285-mimics group (transfected with miR-1285-mimics), miR-1285-mimics+yes-associated protein 1 (YAP1) group (transfected with miR-1285 mimics and YAP1 overexpressed sequence). Stable transfected cells of each group were tested for relative expression level of miR-1285 by qRT-PCR, for cells migration ability by scratch test, for cells invasion ability by Transwell test, and for the expression levels of YAP1, E-cadherin and vimentin protein by Western blotting. **Results** The relative expression levels of miR-1285 were obviously higher in miR-1285-mimics group and miR-1285-mimics+YAP1 group than those in control group and miR-1285-NC group ( $P<0.05$ ), while no significant difference when compared between control group and miR-1285-NC group and between miR-1285-mimics group and miR-1285-mimics+YAP1 group ( $P>0.05$ ). The wound healing rate and the number of transmembrane cells were decreased in miR-1285-mimics group and miR-1285-mimics+YAP1 group than those in control group and miR-1285-NC group ( $P<0.05$ ); among which the wound healing rate was obviously higher and much more transmembrane cells in miR-1285-mimics+YAP1 group than those in miR-1285-mimics group ( $P<0.05$ ). The relative expression levels of YAP1 and Vimentin protein decreased and of E-cadherin protein increased in miR-1285-mimics group and miR-1285-mimics+YAP1 group than those in control

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group and miR-1285-NC group ( $P<0.05$ ); while the relative expression levels of YAP1 and Vimentin protein were obviously higher and of E-cadherin protein markedly lower in miR-1285-mimics+YAP1 group than those in miR-1285-mimics group ( $P<0.05$ ). No significant difference existed between miR-1285-NC group and control group on the wound healing rate, number of transmembrane cells and the relative expression levels of YAP1, Vimentin protein and E-cadherin protein ( $P>0.05$ ). **Conclusion** Overexpression of miR-1285 may inhibit the migration and invasion of ovarian cancer cells by down-regulating the expression level of YAP1.

**[Key words]** ovarian cancer; microRNA-1285; yes-associated protein 1; invasion; migration

卵巢癌是女性常见的生殖系统恶性肿瘤之一，发病率和病死率均较高，严重危害女性的健康。卵巢癌的早期症状隐匿，尚无特异性诊断指标<sup>[1]</sup>，多数患者确诊时已发展至晚期并伴随肿瘤转移，给临床治疗造成了一定困难<sup>[2]</sup>。卵巢癌的主要特征是肿瘤细胞快速生长及向远处转移，肿瘤细胞广泛浸润及转移是造成患者死亡的主要原因<sup>[3]</sup>。微小RNA(miRNA, miR)是一类不具备编码蛋白质能力的小分子RNA，但可在转录水平参与多个基因的调控，发挥癌基因或抑癌基因的作用，与肿瘤细胞的增殖、转移及侵袭过程密切相关<sup>[4]</sup>。卵巢癌患者体内多个miRNA表达失调，可能参与了卵巢癌的发生发展过程。miR-1285是一种高度保守的miRNA，在多种肿瘤细胞中异常表达，主要通过调节下游基因以及抑制肿瘤细胞增殖、侵袭及迁移等而发挥抑癌作用<sup>[5]</sup>。但目前关于miR-1285在卵巢癌中的作用研究尚少，本研究对人卵巢癌OVCAR3细胞转染miR-1285，过表达后观察细胞侵袭及迁移能力，探讨miR-1285对细胞的影响及可能机制，以期为临床治疗卵巢癌提供新的靶点。

## 1 材料与方法

**1.1 材料** 人卵巢癌OVCAR3细胞购自中国科学院上海细胞库。Lipofectamine<sup>TM</sup> 2000试剂盒(美国Invitrogen公司)，含miR-1285拟似物(miR-1285-mimics)、无义随机序列(miR-1285-NC)、过表达Yes相关蛋白1(yes-associated protein 1, YAP1)的pcDNA3.1重组质粒(上海吉玛制药技术有限公司)，Transwell细胞培养小室(美国Corning公司)，兔抗人YAP1单抗、E钙黏蛋白(E-cadherin)多抗、波形蛋白单抗(美国Cell Signaling Technology公司)，HRP标记的山羊抗兔二抗(美国Abcam公司)，DYY-6C电泳仪(北京六一仪器厂)。

### 1.2 方法

**1.2.1 细胞培养** 将OVCAR3细胞置于含10%胎牛血清+100 U/ml青霉素+100 μg/ml链霉素的DMEM培养基中，于5%CO<sub>2</sub>、37℃条件下常规培养。2~3 d传代一次，取对数生长期细胞用于实验。

**1.2.2 细胞转染及分组** 将OVCAR3细胞随机分为miR-1285-mimics组、miR-1285-NC组、miR-

1285-mimics+YAP1组、对照组。转染前1 d，调整细胞密度为 $1 \times 10^6$ 个/ml，接种于6孔板，待细胞融合达80%时进行转染。按照Lipofectamine<sup>TM</sup> 2000说明书步骤，miR-1285-mimics组、miR-1285-NC组和miR-1285-mimics+YAP1组细胞分别转染含有miR-1285-mimics、miR-1285-NC和miR-1285-mimics+YAP1序列的质粒脂质体复合物，对照组仅加入Lipofectamine<sup>TM</sup> 2000。转染48 h后置于荧光显微镜下观察转染效率。

**1.2.3 qRT-PCR法检测细胞中miR-1285的相对表达水平** 取稳定转染的各组细胞，Trizol法提取细胞总RNA，反转录为cDNA。配制反应体系：包括正反向引物各0.5 μl，cDNA模板2 μl，PCR Master Mix 10 μl，加双蒸水至总体积20 μl。扩增条件：95℃预变性10 min；95℃变性20 s、55℃退火30 s、70℃延伸30 s，共进行35个循环。以U6为内参照，采用2<sup>-ΔΔCt</sup>法计算miR-1285的相对表达水平，引物序列见表1。

表1 引物序列

Tab.1 Primer sequence

| 基因       | 引物序列                              |
|----------|-----------------------------------|
| miR-1285 | 正向: 5'-ACGATCGATCGATGCTAGCTACA-3' |
|          | 反向: 5'-CCATGCATGCATGCATGCTAGCA-3' |
| U6       | 正向: 5'-AGCTAGCTAGCTAGCTAGCTAA-3'  |
|          | 反向: 5'-ACGCTAGCTAGCCAGCTAGCTCA-3' |

**1.2.4 划痕实验检测细胞迁移能力** 取稳定转染的各组细胞，调整细胞密度为 $1 \times 10^6$ 个/ml，接种于6孔板，待各组细胞铺满板底时弃去培养基，用灭菌移液枪头在孔中间垂直划一条竖线，PBS洗去划下的细胞，显微镜下拍照，记录初始划痕距离，继续培养24 h后，观察各组细胞的愈合状态。划痕愈合率(%)=(初始划痕距离-24 h划痕距离)/初始划痕距离×100%。

**1.2.5 Transwell实验检测细胞侵袭能力** 用不含血清的DMEM培养基按1:2比例稀释Matrigel胶，放入培养箱中，于37℃静置30 min取出，将Matrigel胶铺在Transwell小室上室，重悬细胞为 $5 \times 10^5$ 个/ml，取100 μl细胞悬液接种于上室，下室加入600 μl含10%胎牛血清的DMEM培养基，常规培养24 h，4%甲醛固定10 min，0.1%结晶紫染色5 min，显微镜下任意

选取5个视野，记录穿膜细胞数，取平均值。

**1.2.6 Western blotting法检测细胞中YAP1、E-cadherin、波形蛋白的相对表达水平** 取稳定转染的各组细胞，加入RIPA裂解液，提取各组细胞总蛋白，BCA法测定蛋白浓度，进行SDS-PAGE凝胶电泳，转至PVDF膜上，5%脱脂牛奶室温封闭2h，加入YAP1、E-cadherin、波形蛋白一抗(1:2000)4℃孵育过夜，TBST洗膜，加入HRP标记的二抗(1:5000)室温孵育1h，TBST洗膜，采用ECL放射自显影，Image J软件分析图像，以β-actin为内参，以目的蛋白条带灰度值与内参条带灰度值的比值作为

目的蛋白的相对表达水平。

**1.3 统计学处理** 采用SPSS 25.0软件进行分析。计量资料以 $\bar{x} \pm s$ 表示，多组间比较采用单因素方差分析，进一步两两比较采用LSD-*t*检验。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

**2.1 各组细胞转染效率比较** 荧光显微镜下，miR-1285-mimics组、miR-1285-NC组及miR-1285-mimics+YAP1组的细胞均有荧光蛋白表达，转染效率>85%，可用于后续实验(图1)。

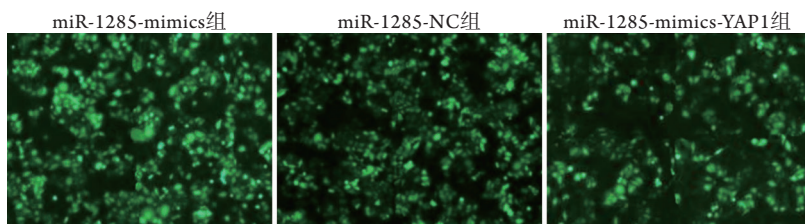


图1 各组卵巢癌OVCAR3细胞转染效率(荧光显微镜 × 200)

Fig.1 Transfection efficiency of ovarian cancer OVCAR3 cells in each group (Fluorescence microscope × 200)

**2.2 各组细胞中miR-1285相对表达水平比较** 对照组、miR-1285-NC组、miR-1285-mimics组、miR-1285-mimics+YAP1组miR-1285相对表达水平分别为 $0.26 \pm 0.06$ 、 $0.28 \pm 0.07$ 、 $1.36 \pm 0.11$ 、 $1.31 \pm 0.10$ ，差异有统计学意义( $F=247.424$ ， $P < 0.001$ )；与对照组、miR-1285-NC组比较，miR-1285-mimics组、miR-1285-mimics+YAP1组miR-1285相对表达水平明显升高，差异有统计学意义( $P < 0.001$ )；对照组与miR-1285-NC组、miR-1285-mimics组与miR-1285-mimics+YAP1组miR-1285相对表达水平比较差异无统计学意义( $P > 0.05$ )。

mimics+YAP1组划痕愈合率分别为 $(83.26 \pm 8.45)\%$ 、 $(82.94 \pm 8.33)\%$ 、 $(42.58 \pm 6.17)\%$ 、 $(62.36 \pm 7.15)\%$ ，差异有统计学意义( $F=32.868$ ， $P < 0.001$ )。与对照组、miR-1285-NC组比较，miR-1285-mimics组、miR-1285-mimics+YAP1组划痕愈合率降低，差异有统计学意义( $P < 0.001$ )；miR-1285-mimics+YAP1组划痕愈合率高于miR-1285-mimics组( $P < 0.001$ )。对照组与miR-1285-NC组划痕愈合率比较差异无统计学意义( $P > 0.05$ ，图2)。

**2.3 各组细胞迁移能力比较** 对照组、miR-1285-NC组、miR-1285-mimics组、miR-1285-

**2.4 各组细胞侵袭能力比较** 对照组、miR-1285-NC组、miR-1285-mimics组、miR-1285-mimics+YAP1组穿膜细胞数分别为 $(286.59 \pm 27.36)$ 个、 $(276.28 \pm 26.74)$ 个、 $(87.42 \pm 15.63)$ 个、

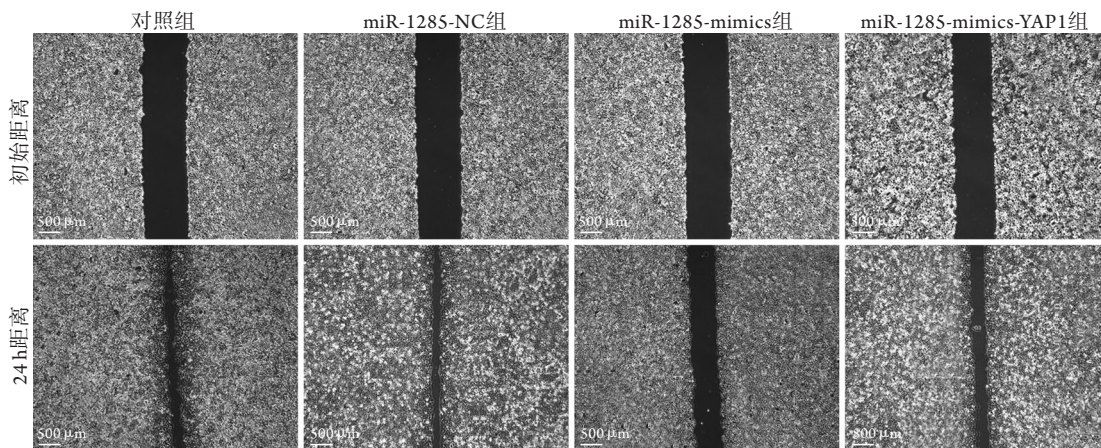


图2 各组卵巢癌OVCAR3细胞迁移能力比较(划痕实验 × 100)

Fig.2 Comparison of cell migration ability of ovarian cancer OVCAR3 cells in each group (Scratch test × 100)

( $162.54 \pm 18.49$ )个, 差异有统计学意义( $F=180.470$ ,  $P<0.05$ )。与对照组、miR-1285-NC组比较, miR-1285-mimics组、miR-1285-mimics+YAP1组穿膜细胞数明显减少( $P<0.001$ ); miR-1285-mimics+YAP1组穿

膜细胞数明显多于miR-1285-mimics组( $P<0.001$ )。对照组与miR-1285-NC组穿膜细胞数比较差异无统计学意义( $P>0.05$ , 图3)。

2.5 各组细胞中YAP1、E-cadherin、波形蛋白相

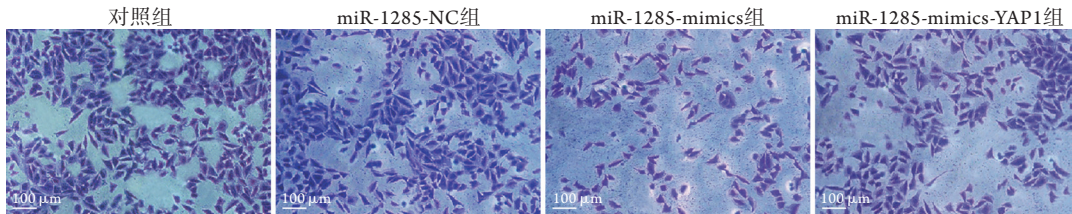


图3 各组卵巢癌OVCAR3细胞侵袭能力比较(Transwell)

Fig.3 Comparison of invasion ability of ovarian cancer OVCAR3 cells in each group (Transwell)

对表达水平比较 Western blotting检测结果显示, 4组细胞中YAP1、E-cadherin、波形蛋白相对表达水平差异有统计学意义( $P<0.05$ )。与对照组、miR-1285-NC组比较, miR-1285-mimics组、miR-1285-mimics+YAP1组YAP1、波形蛋白相对表达水平降低, E-cadherin蛋白相对表达水平升高, 差异有统计学意义( $P<0.05$ ); miR-1285-mimics+YAP1

组YAP1、波形蛋白相对表达水平高于miR-1285-mimics组, E-cadherin蛋白相对表达水平低于miR-1285-mimics组, 差异有统计学意义( $P<0.05$ )。对照组与miR-1285-NC组的YAP1、E-cadherin、波形蛋白相对表达水平比较差异均无统计学意义( $P>0.05$ , 表2, 图4)。

表2 各组卵巢癌OVCAR3细胞中YAP1、E-cadherin、波形蛋白相对表达水平比较( $\bar{x} \pm s$ ,  $n=5$ )

Tab.2 Comparison of relative expression levels of YAP1, E-cadherin and Vimentin protein in each group of ovarian cancer OVCAR3 cells ( $\bar{x} \pm s$ ,  $n=5$ )

| 组别                    | YAP1                        | E-cadherin                  | 波形蛋白                        |
|-----------------------|-----------------------------|-----------------------------|-----------------------------|
| 对照组                   | $1.15 \pm 0.12$             | $0.21 \pm 0.05$             | $1.13 \pm 0.12$             |
| miR-1285-NC组          | $1.12 \pm 0.11$             | $0.23 \pm 0.05$             | $1.15 \pm 0.11$             |
| miR-1285-mimics组      | $0.36 \pm 0.07^{(1)(2)}$    | $0.97 \pm 0.09^{(1)(2)}$    | $0.34 \pm 0.07^{(1)(2)}$    |
| miR-1285-mimics+YAP1组 | $0.89 \pm 0.10^{(1)(2)(3)}$ | $0.61 \pm 0.06^{(1)(2)(3)}$ | $0.78 \pm 0.09^{(1)(2)(3)}$ |
| F                     | 64.573                      | 157.874                     | 73.148                      |
| P                     | $<0.001$                    | $<0.001$                    | $<0.001$                    |

与对照组比较, (1) $P<0.05$ ; 与miR-1285-NC组比较, (2) $P<0.05$ ; 与miR-1285-mimics组比较, (3) $P<0.05$ 。

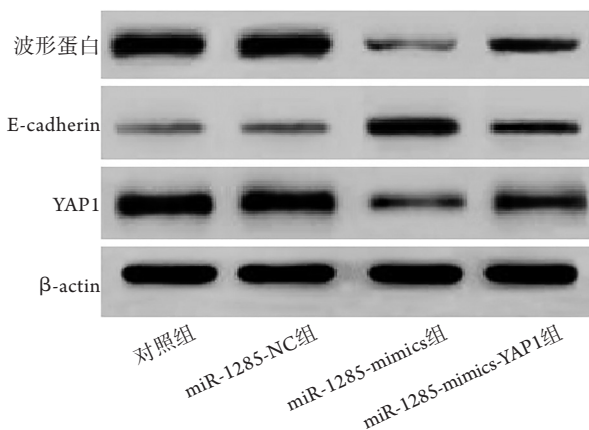


图4 各组卵巢癌OVCAR3细胞中YAP1、E-cadherin、波形蛋白的表达(Western blotting)

Fig.4 Expression of YAP1, E-cadherin and Vimentin protein in each group of ovarian cancer OVCAR3 cells (Western blotting)

3 讨 论

卵巢癌的病死率居妇科肿瘤第一位, 目前临床上主要采用糖类抗原-125(CA-125)及人附睾蛋白作为血清标志物进行联合检查, 但因为这两种标志物在子宫内膜异位等妇科疾病及其他肿瘤中也可升高, 导致其诊断卵巢癌的灵敏度较低, 无法使卵巢癌患者获得早期准确诊断, 错过了治疗的最佳时机<sup>[6-7]</sup>。近年来, 卵巢癌的手术及化疗技术不断改进, 提高了患者的生存率, 但由于化疗耐药性及患者个体差异的存在, 根治性手术及术后化疗的效果仍不理想, 卵巢癌晚期患者术后仍有高达80%的复发率, 因此, 寻找可靠的生物标志物对患者预测预后具有重要意义<sup>[8-9]</sup>。miRNA表达失调与多种肿瘤的发生发展密切相关, 且在不同肿瘤中发挥不同的作用, 对肿瘤的诊断、治疗及预后具有重要意义。

miR-1285最早被发现于人类胚胎干细胞中, 可

与p53特异性结合,通过调节p53的表达水平而发挥对肿瘤细胞的抑制作用<sup>[10]</sup>。本研究为探讨miR-1285对卵巢癌细胞侵袭及迁移的影响,将细胞转染miR-1285拟似物,结果显示,miR-1285-mimics组细胞的miR-1285相对表达水平明显高于对照组及miR-1285-NC组,与以往研究发现卵巢癌组织中miR-1285表达水平明显低于癌旁组织的结果一致<sup>[11]</sup>,表明miR-1285在卵巢癌细胞中低表达,参与了卵巢癌的发生发展过程。本研究还发现,转染miR-1285后细胞的侵袭及迁移能力下降,提示过表达miR-1285可能参与了抑制卵巢癌细胞侵袭及迁移的过程,从而发挥抑癌作用。以往研究发现,miR-1285在早期肺鳞状细胞癌患者血清中的表达水平较低,可作为其早期诊断的分子标志物<sup>[12]</sup>。miR-1285在结直肠癌细胞中异常低表达,可通过调控下游相关基因抑制细胞增殖,促进细胞凋亡,从而发挥抑癌作用<sup>[13]</sup>。本研究发现,卵巢癌细胞中miR-1285表达水平较低,与其他肿瘤中的研究结果一致,提示miR-1285可能参与了卵巢癌的发生发展过程,并与卵巢癌细胞的侵袭及迁移有关。

上皮间质转化(epithelial-mesenchymal transition, EMT)是肿瘤细胞发生侵袭及迁移的关键途径,发生EMT的肿瘤细胞侵袭、迁移及抗凋亡能力增强,表现为上皮细胞标志物E-cadherin等表达下调,间质标志物波形蛋白等表达上调<sup>[14-15]</sup>。YAP1是一种癌蛋白,在胰腺癌、食管癌中异常高表达,对肿瘤细胞的增殖、转移及生存能力具有促进作用,并可提高肿瘤细胞的抗凋亡能力及耐药性<sup>[16-18]</sup>。本研究转染miR-1285拟似物后,miR-1285-mimics组细胞E-cadherin表达上调,波形蛋白表达下调,提示miR-1285可阻止卵巢癌细胞发生EMT,从而阻止细胞发生侵袭及迁移。为探讨miR-1285影响卵巢癌细胞EMT及侵袭、迁移的作用机制,本研究同时转染过表达YAP1序列,结果发现在过表达miR-1285(miR-1285-mimics组)的卵巢癌细胞中,YAP1蛋白表达水平明显低于对照组,细胞侵袭及迁移能力增强,而通过转染过表达YAP1序列(miR-1285-mimics+YAP1组)后,YAP1蛋白表达明显升高,同时细胞的侵袭及迁移能力明显下降,提示miR-1285抑制卵巢癌细胞侵袭及迁移的机制可能是通过调控YAP1发挥作用的。Hu等<sup>[19]</sup>发现,过表达YAP1可逆转miR-1285对骨肉瘤细胞增殖及侵袭的抑制作用,miR-1285通过靶向抑制YAP1蛋白而发挥对骨肉瘤细胞增殖及侵袭的抑制作用。Huang等<sup>[20]</sup>发现,miR-1285在胰腺癌细胞中通过负调控YAP1充当肿瘤抑制剂,抑制肿瘤细胞的增殖、侵袭及迁移。本研究分别转染miR-1285及YAP1,结果显示miR-1285参与了

YAP1蛋白表达的调控,可能通过调控YAP1蛋白相对表达水平而发挥抑癌作用。

综上所述,卵巢癌OVCAR3细胞中miR-1285表达水平较低,过表达miR-1285可抑制OVCAR3细胞的侵袭及迁移,其机制可能是通过调节YAP1蛋白的表达而发挥作用,为miR-1285在临床用于卵巢癌的分子靶向治疗提供了理论依据。但本研究仅在体外细胞水平证实miR-1285对卵巢癌细胞的影响,其体内功能验证及其他调控机制尚需进一步研究。

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