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· 临床研究 ·

miR-1297 通过下调 TET3 促进乳腺癌 MCF-7 细胞的恶性生物学行为

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[摘要] **目的:** 探讨 miR-1297 对乳腺癌细胞恶性生物学行为的调控作用及其潜在机制。**方法:** 选用 2016 年 5 月至 2018 年 5 月乐山市人民医院甲乳外科手术切除的 20 例乳腺癌组织和癌旁组织标本以及乳腺癌细胞系 MCF-7、SW626、HCC1937 和人乳腺上皮细胞 MCF-10A, 用 qPCR 检测乳腺癌组织和细胞系中 miR-1297 的表达水平。实验分为对照组、miR-1297 inhibitor 组、TET 甲基胞嘧啶双加氧酶 3 (TET3) 过表达组及同时过表达 TET3 和 miR-1297 组, 用 CCK-8、Transwell 实验检测 MCF-7 细胞的增殖、迁移和侵袭能力, 用 WB 检测 MCF-7 细胞中 TET3 和 EMT 相关蛋白 (E-cadherin、N-cadherin 和 vimentin) 的表达水平。用双荧光素酶报告基因验证 miR-1297 与 TET3 的靶向关系。**结果:** miR-1297 在乳腺癌组织和细胞系中均高表达 ($P < 0.01$ 或 $P < 0.05$)。敲降 miR-1297 后, MCF-7 细胞的增殖、迁移、侵袭和 EMT 均明显受到抑制 ($P < 0.05$ 或 $P < 0.01$)。转染 pcDNA3.1-TET3 后, MCF-7 细胞 TET3 的表达水平显著上调 ($P < 0.05$); 同时过表达 TET3 和 miR-1297 能够逆转 MCF-7 细胞中 TET3 的表达水平及 TET3 对 MCF-7 细胞增殖、迁移、侵袭和 EMT 的抑制作用。双荧光素酶报告基因结果显示, miR-1297 靶向结合 TET3 的 3' UTR, miR-1297 靶向下调 TET3 从而促进 MCF-7 细胞的恶性生物学行为。**结论:** miR-1297 在乳腺癌组织和细胞中高表达, 其通过靶向下调 TET3 的表达水平促进 MCF-7 细胞增殖、迁移、侵袭和 EMT 等恶性生物学行为。

[关键词] 乳腺癌; MCF-7 细胞; miR-1297; TET3; 上皮间质转化; 增殖; 侵袭; 迁移

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miR-1297 promotes malignant biological behaviors of breast cancer MCF-7 cells by down-regulating TET3

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[Abstract] **Objective:** To investigate the regulatory effect of miR-1297 on the malignant biological behaviors of breast cancer cells and its underlying mechanism. **Methods:** Twenty pairs of breast cancer tissues and para-cancer tissues resected at the Department of Thyroid and Breast Surgery of Leshan People's Hospital from May 2016 to May 2018, as well as breast cancer cell lines MCF-7, SW626, HCC1937 and human breast epithelial MCF-10A cells were collected for this study. qPCR was performed to evaluate the expression of miR-1297 in breast cancer tissues and cell lines. The experimental cells were divided into control group, miR-1297 inhibitor group; TET3 over-expression group and simultaneous over-expression of TET3 and miR-1297 group. CCK-8 assay was used to detect the cell proliferation of MCF-7 cells; Transwell assay was carried out to detect the migration and invasion of MCF-7 cells; and WB was used to measure the expressions of TET3 and EMT related proteins (E-cadherin, N-cadherin and vimentin). Dual luciferase reporter gene assay was used to verify the relationship between miR-1297 and TET3. **Results:** miR-1297 was up-regulated in both breast cancer tissues and cell lines ($P < 0.01$ or $P < 0.05$). Knockdown of miR-1297 dramatically repressed the proliferation, migration, invasion and EMT of MCF-7 cells ($P < 0.01$ or $P < 0.05$). Over-expression of TET3 significantly up-regulated the expression of TET3 in MCF-7 cells ($P < 0.05$). Simultaneous over-expression of TET3 and miR-1297 could reverse the expression level of TET3 in MCF-7 cells and the inhibitory effect of TET3 on the proliferation, migration, invasion and EMT of MCF-7 cells. Dual luciferase reporter gene assay results showed that miR-1297 targetedly bound to the 3' UTR of TET3. Further experiment results demonstrated that miR-1297 targetedly down-regulated TET3 and promoted the malignant biological behaviors of MCF-7 cells. **Conclusion:** miR-1297 is up-regulated in breast cancer tissues and cells; it promotes the malignant biological behaviors such as proliferation, migration, invasion and EMT through targetedly down-regulating the expression of TET3.

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乳腺癌是全世界女性中最常见的恶性肿瘤,也是女性肿瘤死亡的主要原因。乳腺癌细胞增殖和EMT是肿瘤复发的重要因素^[1],因此探究调控乳腺癌细胞EMT发展的机制有助于预防乳腺癌的复发。研究^[2-4]证实,微小RNA(microRNA, miRNA)与肿瘤EMT发展密切相关。miR-1297通过靶向下调AEG-1抑制宫颈癌EMT和转移^[5]。miR-1297在乳腺癌组织和细胞中高表达,且能够促进乳腺癌的增殖^[6],但miR-1297是否能够调控乳腺癌EMT尚不清楚。TET(ten-eleven translocation)甲基胞嘧啶双加氧酶3(TET methylcytosine dioxygenase 3, TET3)是DNA去甲基化过程中的一种重要酶。据报道,过表达TET3可以抑制卵巢癌细胞中TGF- β 1诱导的EMT^[7],TET3表达降低与乳腺癌患者预后差相关^[8]。但miR-1297是否通过调控TET3影响乳腺癌细胞EMT进程尚未见文献报道。本研究通过检测乳腺癌组织与细胞中miR-1297表达及其对乳腺癌MCF-7细胞增殖、迁移、侵袭和EMT相关蛋白表达的影响,旨在探讨miR-1297通过调控TET3影响乳腺癌EMT发展的分子机制。

1 资料与方法

1.1 组织标本、细胞系及主要试剂

收集2016年5月至2018年5月乐山市人民医院乳腺外科手术的20例乳腺癌患者乳腺癌组织和相应癌旁组织标本,取材后迅速存储于液氮中。病例纳入标准:经患者的临床表现及病史、体格检查、影像学检查、组织病理学和细胞病理学检查确诊为乳腺癌。病例排除标准:患者不同意采集样本、患有免疫缺陷疾病和经过放化疗。所有患者均签署知情同意书,研究方案经所在医院伦理委员会批准。

乳腺癌细胞系MCF-7、SW626和HCC1937以及人正常乳腺上皮细胞MCF-10A均购于中国科学院昆明细胞库。

DMEM、胎牛血清以及青、链霉素购自Gibco公司,miR-1297 mimics/inhibitor和pcDNA3.1-TET3购于吉凯基因化学技术有限公司, RNA提取试剂盒、逆转录试剂盒、qPCR试剂盒以及LipofectamineTM 3000购于赛默飞公司,蛋白提取试剂盒、BCA试剂盒以及SDS-PAGE凝胶制备试剂盒购自贝博公司,抗-TET3、抗-E-cadherin、抗-N-cadherin和抗-vimentin抗体和羊抗兔IgG抗体(Goat Anti-Rabbit IgG H&L)购于Abcam公司,CCK-8检测试剂盒购于默沙克公司,Transwell小室购于美国康宁公司,双荧光素酶报告基因试剂盒和报告基因载体均购自Promega公司,qPCR引物由美吉生物公司合成。

1.2 细胞培养及转染

乳腺癌细胞MCF-7、SW626和HCC1937和乳腺上皮细胞MCF-10A常规培养于含10%胎牛血清、青霉素100 U/ml和链霉素100 μ g/ml的DMEM培养基及37 $^{\circ}$ C、5% CO₂的恒温培养箱中,每2~3 d更换新鲜培养液一次,细胞汇合度达80%左右时进行传代或冻存。

选取对数生长期的MCF-7细胞进行细胞转染。将MCF-7细胞接种于6孔板中于培养箱中培养,待细胞汇合度达到70%左右时进行转染。将miR-1297 mimics、miR-1297 inhibitor、pcDNA3.1-TET3、pcDNA3.1-TET3+miR-1297 mimics分别与LipofectamineTM 3000混合均匀后转染MCF-7细胞,恒温培养箱培养12 h后更换一次新鲜培养液,36 h后检测转染效率并用于后续实验。

1.3 qPCR实验检测乳腺癌组织和细胞系中miR-1297的表达水平

根据RNA提取试剂盒说明书提取组织和细胞系的总RNA,逆转录成cDNA后,按照qPCR试剂盒说明书检测miR-1297表达水平,以U6为内参。引物序列:miR-1297 F为5'-ACACTCCAGCTGGGTCTTCATTCCA-3', R为5'-GTGCAGGGTCCGAGGT-3'; U6 F为5'-CTCGCTTCGGCAGCAC-3', R为5'-AACGCTTCACGAATTTGCGT-3'。qPCR反应条件:95 $^{\circ}$ C预变性30 s,95 $^{\circ}$ C变性10 s,55 $^{\circ}$ C退火45 s,40个循环。采用2^{- $\Delta\Delta$ C_t}法进行计算miR-1297的相对表达量。

1.4 WB实验检测MCF-7细胞中TET3和EMT相关蛋白的表达

根据蛋白提取试剂盒说明书提取各组细胞总蛋白,BCA法测定蛋白浓度和纯度。取30 μ g蛋白样品进行10% SDS-PAGE、转膜,5%脱脂奶粉封闭1 h,弃封闭液,分别加入稀释比例均为1:1 000的抗-TET3、抗-E-cadherin、抗-N-cadherin和抗vimentin一抗,4 $^{\circ}$ C孵育过夜。次日,弃去一抗,TBST清洗后加入羊抗兔IgG二抗(1:2 000)室温孵育2 h,TBST清洗后加入ECL试剂于暗室内曝光,最后在凝胶成像仪上观察,用Image J软件分析蛋白条带的灰度值。

1.5 CCK-8法检测MCF-7细胞的增殖能力

收集转染后的MCF-7细胞,接种至96孔板中,每孔 5×10^4 个细胞,并加入200 μ l完全培养基,每孔设置3个复孔。随后分别培养24、48、72和96 h后,在相同时间点向每个孔中加入10 μ l的CCK-8溶液,继续培养2 h。后用酶标仪检测波长450 nm处的光密度(D)值。

1.6 Transwell检测MCF-7细胞的侵袭和迁移能力

将转染后的各组细胞细胞密度调整为 1×10^5 个/ml, 每组细胞取200 μ l接种于预先用1:8稀释的Matrigel胶包被的Transwell上室中, 并在下室中加入600 μ l完全细胞培养基, 每组设置3个复孔, 置于细胞培养箱中继续培养24 h。后用无菌棉签擦去上室细胞, 用4%多聚甲醛固定下室细胞, 0.1%结晶紫染色10 min, PBS洗涤3次, 最后在显微镜下观察、计数各组穿膜的细胞数。迁移实验Transwell上室不预铺Matrigel胶, 其他实验步骤与侵袭实验一致。

1.7 双荧光素酶报告基因检测miR-1297与TET3靶向关系

将TET3的野生型(Wt)和突变型(Mut)序列克隆到双荧光素酶报告基因质粒载体中, 构建TET3-Wt和TET3-Mut质粒。随后将两种质粒分别与miR-1297 mimics共转染到239T细胞中, 转染48 h后用双荧光素

酶报告基因试剂盒测定试剂盒检测荧光强度。

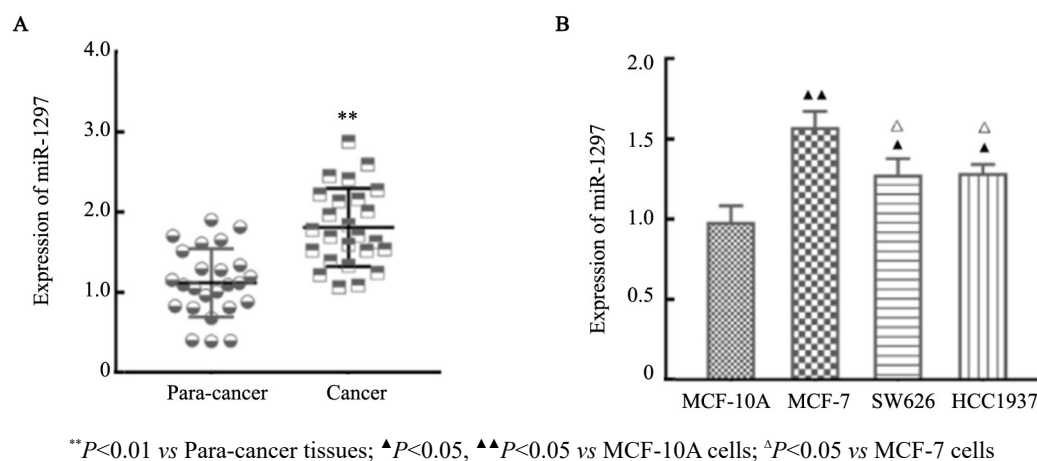
1.8 统计学处理

1.3~1.7实验均重复3次。采用SPSS 12.0统计学软件对实验数据进行分析, 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 miR-1297在乳腺癌组织和细胞系中呈高表达

qPCR检测结果显示, 乳腺癌组织中miR-1297的表达水平明显高于癌旁组织($t=5.345, P < 0.01$; 图1A); MCF-7、SW626和HCC1937细胞中miR-1297表达水平明显高于MCF-10A细胞($t=7.348, 3.674, 4.746, P < 0.05$ 或 $P < 0.01$; 图1B), 以在MCF-7细胞中的表达水平最高($F=11.460, P < 0.01$), 所以后续实验选用该细胞。



** $P < 0.01$ vs Para-cancer tissues; ▲ $P < 0.05$, ▲▲ $P < 0.05$ vs MCF-10A cells; ▲ $P < 0.05$ vs MCF-7 cells
A: Expression of miR-1297 in breast cancer tissues; B: Expression of miR-1297 in breast cancer cells

图1 乳腺癌组织和细胞中miR-1297的表达

Fig.1 Expression of miR-1297 in breast cancer tissues and cells

2.2 敲降miR-1297显著抑制MCF-7细胞的增殖、迁移、侵袭及EMT

敲降miR-1297后, 与对照组比较: miR-1297 inhibitor组MCF-7细胞中miR-1297的表达水平显著下调($t=4.899, P < 0.05$; 图2A); miR-1297 inhibitor组MCF-7细胞的增殖能力显著下降($t=5.736, P < 0.05$; 图2B); miR-1297 inhibitor组MCF-7细胞的侵袭及迁移能力显著下降($t=25.060, 27.850$, 均 $P < 0.01$; 图2C); miR-1297 inhibitor组MCF-7细胞中上皮细胞标志物E-cadherin表达水平显著上调($t=24.680, P < 0.01$; 图2D), 间充质细胞标志物N-cadherin和vimentin表达水平显著下调($t=12.84, 14.45$, 均 $P < 0.01$)。结果表明, 敲降miR-1297可以抑制MCF-7细胞增殖、侵袭、迁移和EMT。

2.3 miR-1297靶向下调TET3的表达

通过starBase生物信息网站预测miR-1297与TET3的结合位点, 结果显示TET3的3'-UTR区域存在miR-1297的结合位点(图3A)。双荧光素酶报告基因实验和WB实验结果(图3A、B)显示, TET3野生型质粒组双荧光素酶荧光活性明显低于NC组($t=8.630, P < 0.01$); 且过表达miR-1297显著下调MCF-7细胞中TET3的表达水平($t=6.228, P < 0.05$)。结果表明, miR-1297负向调控TET3的表达。

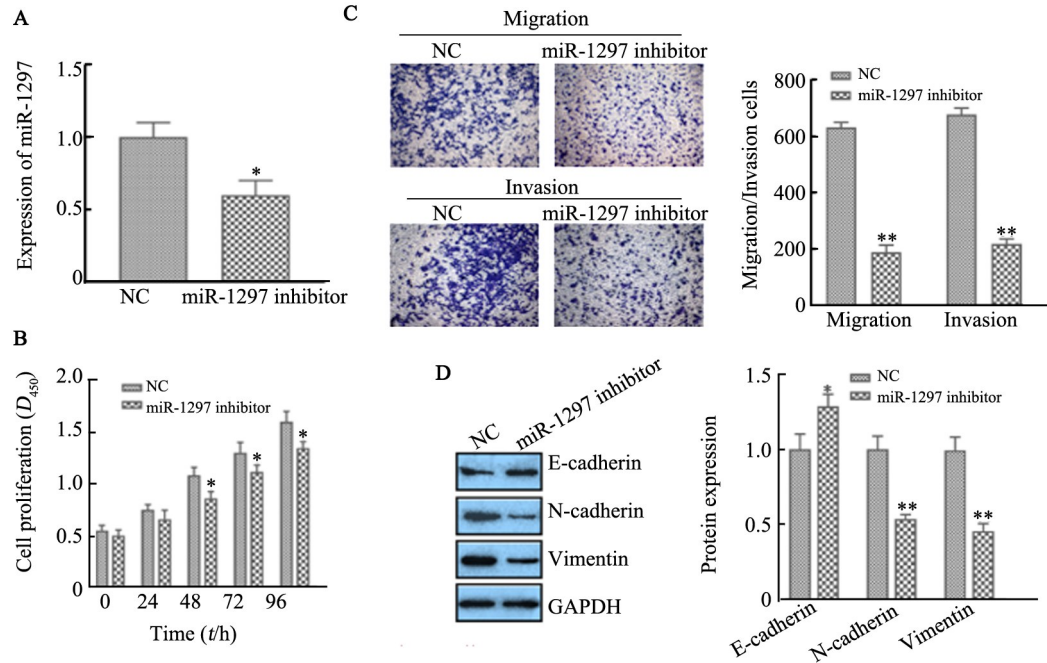
2.4 miR-1297通过调控TET3促进MCF-7细胞增殖、迁移、侵袭和EMT

与NC组比较, pcDNA3.1-TET3组MCF-7细胞中TET3的表达水平显著上调($P < 0.05$), 同时过表达TET3和miR-1297能够逆转MCF-7细胞中TET3的

表达水平(图4A)。过表达TET3可抑制MCF-7细胞的增殖,同时过表达TET3和miR-1297可逆转TET3的抑制作用(图4B)、还可逆转TET3对MCF-7细胞的迁移和侵袭的作用(图4C)。

过表达TET3,可上调MCF-7细胞中E-cadherin、

下调N-cadherin和vimentin表达水平;同时过表达TET3和miR-1297,可以逆转上述的对EMT相关蛋白表达的调控作用(图4D)。结果表明,miR-1297通过下调TET3促进MCF-7细胞的增殖、侵袭、迁移和EMT。

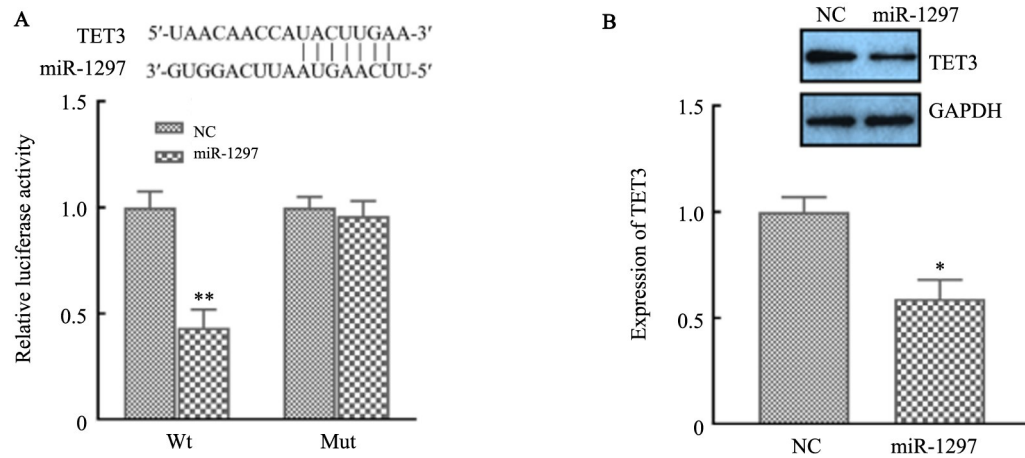


*P<0.05,**P<0.01 vs NC group

A: qPCR was used to detect the expression of miR-1297; B: The cell proliferation of MCF-7 cells was evaluated by CCK-8 assay
C: Transwell assay was performed to detect the migration and invasion of MCF-7 cells (crystal violet staining,×40);
D: WB was carried out to measure the expression of E-cadherin, N-cadherin and vimentin

图2 敲降miR-1297对MCF-7细胞增殖、迁移、侵袭和EMT的影响

Fig.2 The impact of miR-1297 silencing on the proliferation, migration, invasion and EMT of MCF-7 cells

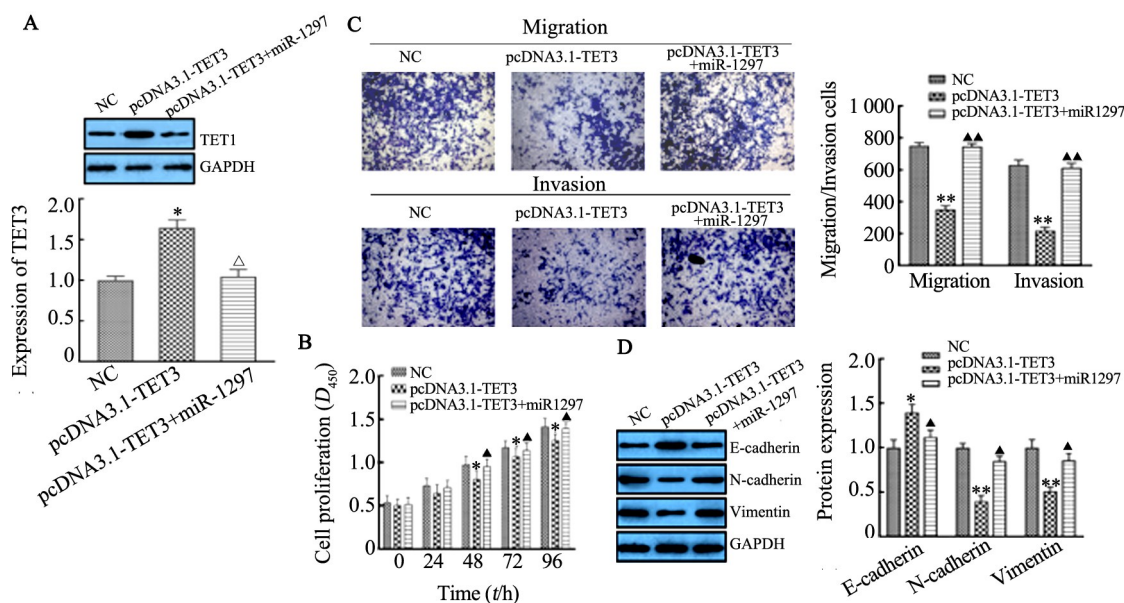


*P<0.05,**P<0.01 vs NC group

A: Dual-luciferase reporter gene was carried to verify the targeted relationship between miR-1297 and TET3;
B: WB was used to detect the expression of TET3

图3 miR-1297和TET3的靶向关系

Fig.3 The targeted relationship between miR-1297 and TET3



* $P < 0.05$, ** $P < 0.01$ vs NC group; $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.05$, $^{\Delta\Delta\Delta}P < 0.01$ vs pcDNA3.1-TET3 group

A and D: WB was carried out to measure the expression of TET3, E-cadherin, N-cadherin and Vimentin;
B: CCK-8 assay was used to detect the cell proliferation of MCF-7 cells; C: Transwell assay was performed to detect the migration and invasion of MCF-7 cells (crystal violet staining, $\times 40$)

图4 miR-1297通过调控TET3对MCF-7细胞恶性生物学行为的影响

Fig.4 The influence of miR-1297 on the malignant biological behaviors of MCF-7 cells via regulating TET3

3 讨论

miRNA在多种肿瘤中异常表达,且参与调控癌细胞增殖、迁移、分化和凋亡等多种恶性生物学行为,在肿瘤发展过程中发挥重要作用。例如,miR-493-5p在乳腺癌细胞中低表达,过表达miR-493-5p可抑制乳腺癌细胞侵袭和肿瘤发生^[9];miR-383-5p作为抑癌基因在肺癌中低表达,且可作为肺癌预后标志物,抑制肺癌细胞增殖^[10]。miR-1297在不同的肿瘤中分别扮演抑癌和致癌基因的作用:CHEN等^[11]研究表明,miR-1297作为抑癌基因在胰腺癌中低表达,且过表达miR-1297靶向下调MTDH抑制胰腺癌细胞增殖和迁移;GAO等^[12]报道,下调miR-1297与胃癌患者预后较差相关,且促进胃癌细胞增殖;但也有学者报道,miR-1297可以促进非小细胞肺癌细胞增殖^[13]和宫颈癌发展^[14]。同时有报道^[6]显示,miR-1297在乳腺癌中高表达。本研究也发现,miR-1297在乳腺癌组织和细胞系中高表达,且在MCF-7细胞中表达水平最高,因此本研究选择该株细胞进行后续实验。结果发现,敲降miR-1297显著抑制乳腺癌MCF-7细胞的增殖、迁移、侵袭和EMT等恶性生物学行为,说明高水平的miR-1297可能与乳腺癌的发展有关。

TET通过氧化作用将5-甲基胞嘧啶修饰为5-羟甲基胞嘧啶^[15-17]。研究^[18-20]表明,TET家族蛋白在乳

腺癌、肝癌、胶质细胞瘤和黑色素瘤等多种恶性肿瘤中异常表达。例如,外源性沉默TET2和TET3能够诱导黑色素瘤细胞EMT进程^[20];TET3通过去甲基化miR-30d前体基因的表达抑制卵巢癌细胞中TGF- β 1诱导的EMT^[7];TET3作为TET家族成员之一,在乳腺癌中低表达,其表达水平降低与乳腺癌患者预后较差密切相关^[8]。本研究发现,miR-1297能够特异性结合TET3的3'-UTR区域,且过表达miR-1297能够下调TET3的表达水平。结果说明,TET3是miR-1297的下游靶基因,miR-1297可能通过TET3调控乳腺癌的发展进程。进一步研究证实,miR-1297可以通过靶向下调TET3的表达水平促进乳腺癌MCF-7细胞增殖、迁移、侵袭和EMT。

综上所述,miR-1297在乳腺癌组织和细胞中高表达,可以作用乳腺癌早期诊断的生物标志物,其机制可能为miR-1297通过靶向下调TET3的表达水平进而促进MCF-7细胞增殖、迁移、侵袭和EMT等恶性生物学行为。

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