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·基础研究·

miR-143-3p通过靶向EZH2调控结肠癌RKO细胞增殖、迁移和侵袭

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[摘 要] **目的**:探讨miR-143-3p通过靶向果蝇zeste基因增强子同源物2(enhancer of zeste homolog 2, EZH2)调控结肠癌RKO细胞增殖、迁移和侵袭的分子机制。**方法**:选用2015年3月至2017年7月昆明医科大学第一附属医院手术切除的40例结肠癌患者的癌及癌旁组织标本,以及结肠癌细胞系COLO320、RKO、CL-11和正常肠黏膜细胞株NCM460,用qPCR法检测结肠癌组织和细胞系中miR-143-3p的表达水平。分别将miR-143-3p mimics、miR-143-3p inhibitor、EZH2 shRNA及阴性对照质粒转染进RKO细胞,用CCK-8法、Transwell小室法分别检测miR-143-3p/EZH2分子轴对RKO细胞增殖、迁移和侵袭的影响,用Western blotting检测RKO细胞中EZH2蛋白的表达。用双荧光素酶报告基因实验验证miR-143-3p和EZH2的靶向关系。**结果**:miR-143-3p在结肠癌组织和细胞系中均低表达(均P<0.01)。过表达miR-143-3p显著抑制RKO细胞的增殖、迁移和侵袭能力(均P<0.01)。双荧光素酶报告基因实验证实miR-143-3p靶向EZH2。同时敲降miR-143-3p和EZH2可逆转敲降EZH2对RKO细胞增殖、迁移和侵袭能力的抑制作用。**结论**:miR-143-3p通过靶向EZH2并下调其表达水平进而抑制结肠癌细胞的增殖、迁移与侵袭。

[关键词] miR-143-3p;果蝇zeste基因增强子同源物2;结肠癌;RKO细胞;增殖;迁移;侵袭
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miR-143-3p regulates proliferation, migration and invasion of colon cancer RKO cells *via* targeting EZH2

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[Abstract] Objective: To investigate the molecular mechanism of miR-143-3p regulating the proliferation, migration and invasion of colon cancer RKO cells *via* targeting enhancer of zeste homolog 2 (EZH2). **Methods:** A total of 40 pairs of colon cancer tissues and corresponding para-cancerous tissues resected in the First Affiliated Hospital of Kunming Medical University from March 2015 to July 2017 were collected for this study. In addition, colon cancer cell lines (COLO320, RKO and CL-11) and normal intestinal mucosa NCM460 cells were also collected. qPCR was applied to detect the expression level of miR-143-3p in colon cancer tissues and cell lines. miR-143-3p mimics, miR-143-3p inhibitor, EZH2 siRNA and negative control plasmids were transfected into RKO cells, respectively. The effect of miR-143-3p/EZH2 axis on the proliferation, migration and invasion of RKO cells were detected by CCK-8 and Transwell assay, respectively. Western blotting was used to detect the expression level of EZH2 protein in RKO cells. The targeting relationship between miR-143-3p and EZH2 was verified by Dual luciferase reporter gene assay. **Results:** The expression level of miR-143-3p was downregulated in colon cancer tissues and cell lines (all P<0.01). Overexpression of miR-143-3p significantly inhibited the proliferation, migration and invasion of RKO cells (all P<0.01). Dual luciferase reporter gene assay confirmed that EZH2 was a target gene of miR-143-3p. Simultaneous knockdown of miR-143-3p and EZH2 attenuated the inhibition of EZH2 knockdown on the proliferation, migration and invasion of RKO cells. **Conclusion:** miR-143-3p suppresses the proliferation, migration and invasion of colon cancer cells *via* targetedly down-regulating EZH2.

[Key words] miR-143-3p; enhancer of zeste homolog 2 (EZH2); colon cancer; RKO cell; proliferation; migration; invasion
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结肠癌是常见的消化道恶性肿瘤[1-2]，其病死率高的主要原因是结肠癌细胞的恶性增殖和转移[3-4]。因此，靶向结肠癌细胞增殖和转移是治疗结肠癌、提高患者生存率的重要策略。研究表明，微小RNA（microRNA，miRNA）通过调控靶基因表达影响结肠癌细胞的恶性生物学行为。例如，miR-223作为癌基因通过靶向p120促进结肠癌侵袭和转移[5]；敲降miR-19b-3p通过上调SMAD4的表达抑制结肠癌细胞的增殖、迁移并促进其凋亡[6]；过表达miR-487b-3p可下调GRM3的表达抑制结肠癌的发展进程[7]；过表达miR-143-3p可显著抑制结直肠癌细胞的增殖和转移[8]。同时通过在线预测数据库StarBase v2.0分析显示，果蝇zeste基因增强子同源物2（enhancer of zeste homolog 2，EZH2）为miR-143-3p的候选靶基因，参与调控结肠癌细胞的增殖和迁移[9]。然而，有关miR-143-3p靶向EZH2调控结肠癌细胞增殖与转移的机制尚未见文献证实。本研究通过检测结肠癌组织和细胞中miR-143-3p表达水平，探讨miR-143-3p/EZH2分子轴调控结肠癌细胞增殖、迁移和侵袭的分子机制，为结肠癌的治疗提供新的靶点和治疗策略。

1　材料与方法

1.1　组织标本、细胞系及主要试剂

收集2015年3月至2017年7月昆明医科大学第一附属医院手术切除的40例结肠癌患者的癌和癌旁组织标本，迅速保存于液氮中。所有标本均经病理学检查确诊为结肠癌，入院前患者未接受过任何结肠癌的有关治疗，术前均告知患者并签署知情同意书，研究方案已获所在医院伦理委员会的审查批准。

人结肠癌细胞系COLO320、RKO和CL-11以及正常肠黏膜细胞NCM460、慢病毒包装细胞HEK293T细胞均购于欧洲认证细胞收藏中心（ECACC）。

胎牛血清（FBS）及RPMI 1640培养基均购于Thermo Scientific HyClone公司，青霉素和链霉素购于Thermo Fisher Scientific公司，TRIzol试剂盒购于Invitrogen公司，一步法逆转录试剂盒One Step TB Green™ PrimeScript™ RT-PCR Kit购于TaKaRa公司，miR-143-3pmimics、miR143-3p inhibitor和EZH2 shRNA购于Thermo Fisher Scientific公司，全蛋白提取试剂盒购于美国Bio-Rad公司，GAPDH、EZH2一抗和辣根过氧化物酶（horseradish peroxidase，HRP）标记的羊抗兔二抗均购于美国CST公司，ECL化学发光液购于Amersham Pharmacia公司，CCK-8试剂盒购于索莱宝公司，Transwell小室购于美国Corning公司，Lipofectamine™ 3000购于Invitrogen公司，双荧光素酶报告基因试剂盒购于Promega公司。

1.2　细胞培养与转染

将结肠癌COLO320、RKO、CL-11细胞和人正常肠黏膜NCM460细胞置于含10% FBS、100 U/ml青霉素和100 μg/ml链霉素的RPMI 1640培养基中，于37 ℃、5%CO_2培养箱中常规培养。

将RKO细胞于RPMI 1640培养基中培养24 h至细胞汇合度为80%时，分别用Lipofectamine™ 3000将100 nmol/L的miR-143-3p mimics（miR-143-3p）、miR-143-3p inhibitor（miR-143-3p-inh）、EZH2 shRNA（si-EZH2）及阴性对照（miR-NC）转染RKO细胞，于37 ℃、5%CO_2培养箱中培养2~4 d。

1.3　qPCR法检测结肠癌组织和细胞系中miR-143-3p的表达水平

TRIzol试剂盒提取结肠癌组织标本和细胞系中的总RNA。一步法逆转录定量试剂盒进行定量，参考逆转录反应说明书的方法，将RNA逆转录为cDNA。PCR引物序列：miR-143-3p F为5'-GGGGTGAGATGAAGCACTG-3'，R为5'-CAGTGCGTGTCGTGGAGT-3';U6 F为5'-TGTGCTGGAAAATCCAAGTCA-3'，R为5'-CGCTTCACGAATTTGCGTGTCAT-3'。PCR反应条件：42 ℃ 5 min，95 ℃ 10 s；95 ℃ 5 s，60 ℃ 30 s，共40个循环；建立溶解曲线。检测结果采用$2^{-\Delta\Delta Ct}$法进行计算。

1.4　CCK-8法检测RKO细胞的增殖能力

细胞转染0、24、48、72和96 h后，调整各组细胞密度为5×10^4个/ml，分别取100 μl接种于96孔板中，每组设置3个复孔。向每孔加入10 μl CCK-8溶液，于培养箱内继续孵育2 h后，用酶标仪检测波长在450 nm处的光密度（*D*）值。*D*值与活细胞的数量成正比，由此可以检测细胞的增殖活力。

1.5　Transwell小室法检测RKO细胞的迁移和侵袭能力

Transwell培养板上室加入200 μl细胞悬液（细胞密度为1×10^4个/ml），下室加入600 μl含有10%FBS的RPMI 1640培养基，于37 ℃、5%CO_2恒温培养箱中孵育24 h。4%多聚甲醛固定迁移并黏附在微孔膜下面的细胞30 min，0.1%的结晶紫染色30 min。PBS冲洗后，于倒置显微镜下（×200）随机选取5个视野观察计数迁移与侵袭细胞数。细胞侵袭实验需预先用Matrigel胶包被Transwell小室微孔膜，37 ℃放置30 min后加入细胞，其他操作与迁移实验相同。

1.6　双荧光素酶报告基因实验验证miR-143-3p和EZH2的靶向关系

根据EZH2基因的3'-UTR上游引物序列为5'-AATCTCGAGCATCTGCTACCTCC-3'和下游引物序列为5'-CCGCTCGAGTTGCAAAAATTCAC-3'（含*Xho* Ⅰ酶切位点）。经*Xho* Ⅰ酶切并插入pGL3-promoter质粒

载体中。测序鉴定插入序列准备无误后，将该重组质粒命名为pGL3-EZH2-3'-UTR-WT。同时，利用定点突变将EZH2基因3'-UTR的miR-143-3p潜在结合部位5'-GUACCAGUGAAUUUUUGCAAUA-3'序列中划线碱基删除，并将该重组质粒命名为pGL3-EZH2-3'UTR-MUT。然后，采用Lipofectamine™ 3000将miR-143-3p mimics和EZH2野生型载体或突变型载体转入HEK-293T细胞内，将报告质粒和miR-143-3p mimics或miR-NC共转染。每孔加入100 μl裂解缓冲液，然后将培养板放在摇床15 min。将细胞裂解液加入到EP管内，4 ℃ 12 000×*g*离心10 min，将EP管内的上清液转移至新的EP管中。48孔板中加入100 μl荧光素酶检测试剂Ⅱ、20 μl细胞裂解液，测定萤火虫荧光素酶和海肾荧光素酶的活性。以海肾荧光素酶活性作为内参，验证miR-143-3p和EZH2的靶向关系。

1.7 Western blotting检测RKO细胞中EZH2蛋白的表达水平

收集RKO细胞，提取细胞总蛋白，BCA试剂盒检测蛋白浓度及纯度。取20 μg进行SDS-PAGE、转PVDF膜，5%脱脂奶粉室温封闭2 h后，加入EZH2一抗（1∶1 000），4 ℃孵育过夜。次日洗去一抗，加入HRP标记的羊抗兔二抗（1∶5 000），室温封闭1 h后加入ECL化学发光液，于化学发光仪系统中采集图像，用Image J对蛋白条带进行定量分析，以目的蛋白条带灰度值与内参照蛋白GAPDH条带灰度值的比值表示目的蛋白的相对表达水平。

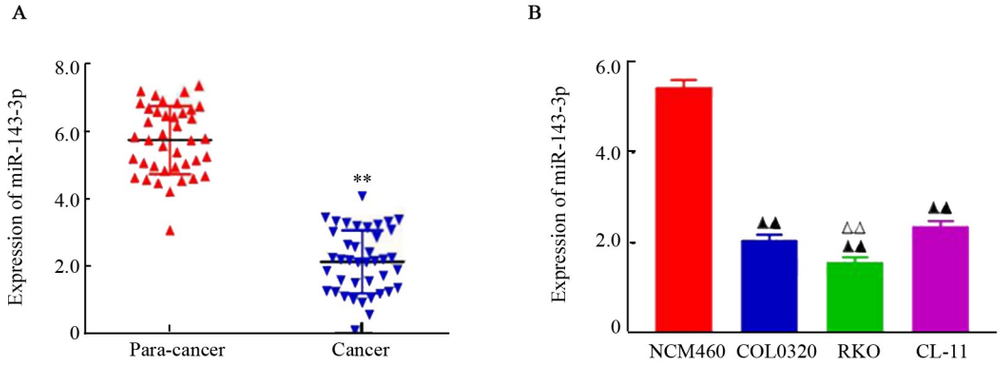
1.8 统计学处理

1.3~1.7实验均重复3次。使用SPSS20统计学软件对实验数据进行统计分析。正态分布的计量数据以$\bar{x}\pm s$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表示差异具有统计学意义。

2 结 果

2.1 miR-143-3p在结肠癌组织和细胞系中均低表达

qPCR法检测结果显示，结肠癌组织中miR-143-3p表达水平显著低于癌旁组织（*t*=18.239，*P*<0.01；图1A）；结肠癌COLO320、RKO、CL-11细胞中miR-143-3p表达水平显著低于NCM460细胞（*t*=19.038、15.497、15.947，均*P*<0.01；图1B），且RKO细胞中miR-143-3p表达水平明显低于COLO320和CL-11细胞（*F*=23.154，*P*<0.01），所以后续转染实验选用RKO细胞。实验结果表明，结肠癌组织和细胞系中miR-143-3p均低表达。



**P<0.01 *vs* Para-cancer tissues; ▲▲P<0.01 *vs* NCM460 cells; △△P<0.01 *vs* COLO320 or CL-11 cells

图1 miR-143-3p在结肠癌组织（A）和细胞系（B）中的表达水平

Fig.1 The expression level of miR-143-3p in colon cancer tissues (A) and cell lines (B)

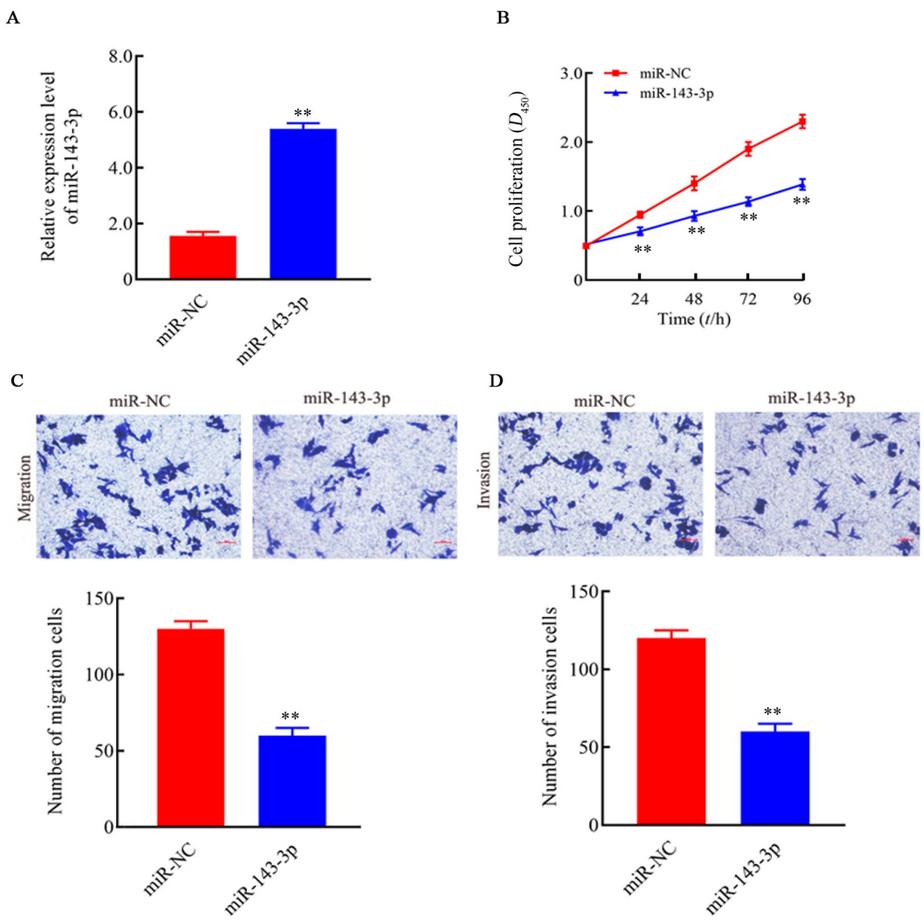
2.2 过表达miR-143-3p抑制结肠癌细胞的增殖、迁移和侵袭能力

qPCR法检测结果显示，转染miR-143-3p mimics后，RKO细胞中miR-143-3p的表达水平显著高于对照组（*t*=26.620，*P*<0.01；图2A）。CCK-8和Transwell实验结果显示，过表达miR-143-3p显著抑制RKO细胞的增殖、迁移和侵袭（增殖：t_{24}=5.715、t_{48}=6.661、t_{72}=11.160、t_{96}=12.540，均*P*<0.01；迁移：*t*=17.150，*P*<0.01；侵袭：*t*=14.170，*P*<0.01；图2B~D）。结果表明，过表达miR-143-3p抑制结肠癌细胞的增殖、迁移和侵袭能力。

2.3 EZH2是miR-143-3p的靶基因

Starbase数据库预测结果（图3A）显示，EZH2可能是miR-143-3p的靶基因。双荧光素酶报告基因实验验证结果（图3B）显示，共转染pmirGLO-EZH2-WT/miR-143-3p mimics的HEK-293T细胞中荧光素酶活性显著低于对照组（*t*=27.139，*P*<0.01），而共转染miR-143-3p mimics/pmirGLO-EZH2-MUT载体的HEK-293T细胞的荧光素酶活性与对照组比较差异无统计学意义（*t*=0.372，*P*>0.05）。Western blotting检

测结果（图3C）显示，过表达miR-143-3p可显著下调RKO细胞中EZH2蛋白的表达水平（t=16.857，P<0.01）。实验结果表明，EZH2是miR-143-3p的靶基因，且miR-143-3p可负调控EZH2表达。



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

图2　过表达miR-143-3p对RKO细胞miR-143-3p表达（A）、增殖（B）、迁移（C）和侵袭（D）的影响（×200）

Fig.2　Effects of miR-143-3p overexpression on the miR-143-3p expression (A), proliferation (B), migration (C) and invasion (D) of RKO cells (×200)

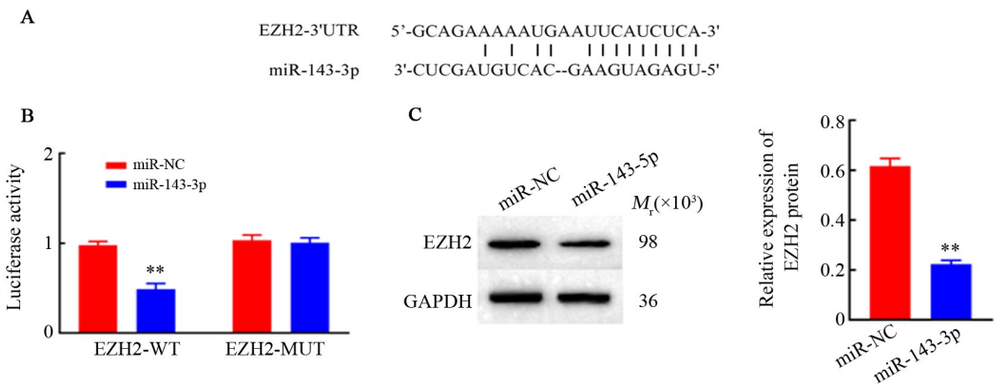
2.4　miR-143-3p通过靶向EZH2调控结肠癌细胞增殖、迁移和侵袭

Western blotting检测结果（图4A）显示，与对照组相比，转染si-EZH2的RKO细胞中EZH2蛋白表达水平显著下调（t=26.895，P<0.01），而同时共转染miR-143-3p inhibitor和si-EZH2的RKO细胞中EZH2蛋白表达水平与对照组比较差异无统计学意义（t=0.433，P>0.05）。CCK-8和Transwell检测结果（图4B~D）显示，敲降EZH2显著抑制RKO细胞增殖、迁移和侵袭（增殖：t_{24}=7.253、t_{48}=21.986、t_{72}=16.510、t_{96}=21.762，均P<0.01；迁移：t=11.258，P<0.01；侵袭：t=21.500，P<0.01）；同时敲降miR-143-3p和EZH2，RKO细胞的增殖、迁移和侵袭与对照组比较差异均无统计学意义（增殖：t_{24}=0.211、t_{48}=0.210、t_{72}=0.212、t_{96}=0.092，均P>0.05；迁移：t=1.890，P>0.05；侵袭：t=0.010，P>0.05）。实验结果表明，miR-143-3p通过靶向EZH2并下调其表达水平，进而抑制结肠癌细胞的增殖、迁移和侵袭能力。

3　讨　论

肿瘤发生的本质是细胞内原癌基因的激活或者抑癌基因的突变或缺失导致细胞恶性增殖和转移。在肿瘤的发展过程中有许多调节因子，它们可以调控癌基因或抑癌基因的表达，促进或抑制肿瘤的发展。大量研究[10]表明，miRNA是参与调控多种肿瘤发生发展的重要基因（如miR-143-3p）。过表达miR-143-3p能够抑制喉部鳞状细胞癌细胞的转移[11]；miR-143-3p作为抑癌基因抑制卵巢癌细胞的增殖和转移[12]；敲降miR-143-3p可以促进乳腺癌细胞增殖[13]。LIU等[14]研究发现，过表达lncRNA ZEB2-AS1通过抑

制miR-143促进结肠癌细胞增殖并抑制细胞凋亡，进而加速结直肠癌的恶性进程。此外，GOMES等[15]研究证实，过表达miR-143通过靶向下调SOD1上调奥沙利铂诱导结肠癌细胞凋亡。本研究结果同样证实，miR-143-3p为抑癌基因，且过表达miR-143-3p能够抑制结肠癌细胞的增殖、迁移和侵袭。

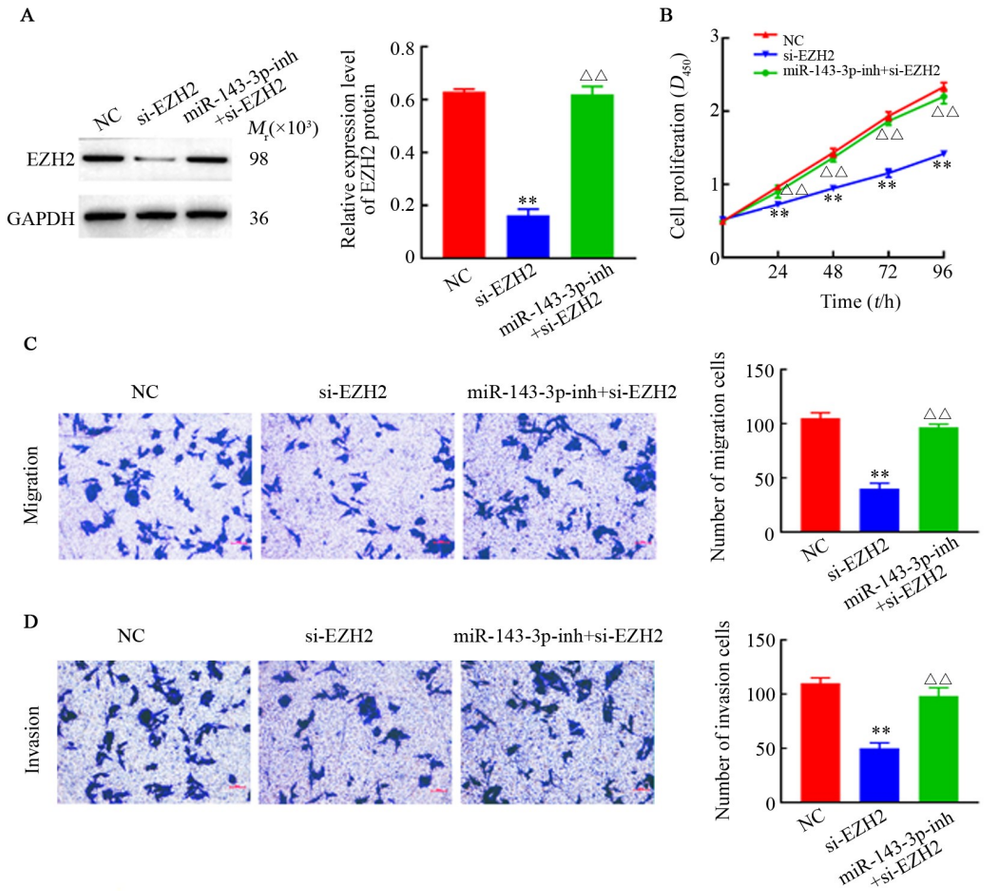


$^{**}P$<0.01 *vs* miR-NC group

A: The bioinformatics analysis result showed that miR-143-3p had a binding site with EZH2; B: Dual luciferase reporter gene assay was used to verify the relationship between miR-143-3p and EZH2; C: Western blotting was used to detect the expression of EZH2

图3 EZH2是miR-143-3p的靶基因

Fig.3 EZH2 was a target gene of miR-143-3p



$^{**}P$<0.01 *vs* NC group; $^{\triangle\triangle}P$<0.01 *vs* si-EZH2 group

A: The expression of EZH2 protein was measured by Western blotting; B: The cell proliferation was measured by CCK-8 assay; C and D: The cell migration an invasion were measured by Transwell assay (×200)

图4 miR-143-3p通过靶向EZH2调控结肠癌细胞的增殖、迁移和侵袭

Fig.4 miR-143-3p regulated the prolferation migration and invasion of colon cancer cells by targeting EZH2

miRNA通过靶向目标基因3'UTR并下调其表达水平，进而调控肿瘤细胞的增殖、侵袭、迁移和凋亡[16-17]。例如，miR-143-3p通过靶向COX-2调控恶性黑色素瘤的发展进程；miR-143-3p/QKI-5分子轴抑制食管癌细胞的增殖与侵袭[18]；miR-143-3p通过下调BCL2表达抑制宫颈癌细胞增殖并促进细胞凋亡[19]。本研究也证实了miRNA/mRNA分子轴调控结肠癌发展这一机制，即miR-143-3p通过靶向癌基因EZH2并下调其表达水平进而抑制结肠癌细胞的增殖、迁移和侵袭。

研究[20]发现，EZH2过表达与结直肠癌细胞的浸润、淋巴结转移和肿瘤分化程度与预后密切相关。同时，也有研究证实EZH2在多种恶性肿瘤中高表达[21]，且敲降EZH2可显著抑制肿瘤细胞的增殖和转移能力[22]。此外，EZH2也受到miRNA的调控，从而介导恶性肿瘤细胞的增殖、侵袭和迁移能力，例如miR-625-3p[23]、miR-506[24]靶向EZH2抑制胃癌、鼻咽癌细胞转移能力。本研究结果同样证实，miR-143-3p靶向下调EZH2抑制结肠癌细胞的增殖、侵袭和迁移能力。

综上所述，本研究深入阐述了通过靶向miR-143-3p上调EZH2表达水平进而促进结肠癌细胞增殖、迁移和侵袭的分子机制。miR-143-3p的表达与结肠癌发生、发展过程密切相关，因此miR-143-3p及其分子轴可以作为新的结肠癌治疗靶点。

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