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miR-205对胃癌细胞侵袭迁移的调控作用及其潜在机制

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miR-205对胃癌细胞侵袭迁移的调控作用及其潜在机制

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Regulatory Effects of miR-205 on Invasion and Migration of Gastric Cancer Cells and Potential Mechanism

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Abstract: Objective To investigate the effect of miR-205 on the invasion and migration of HGC27 cells and related mechanism. **Methods** The expression of miR-205 in four kinds of gastric cancer cell lines (AGS, MKN74, HGC27, SGC7901) were measured by real-time quantitative PCR. miR-205 mimic was transfected into HGC27 cells for up-regulation of miR-205, then cells invasion and migration were detected by scratch test and Transwell assay. Furthermore, epithelial to mesenchymal transition (EMT) progress and the activation of related signal pathway were measured by Western blot. **Results** Real-time quantitative PCR showed that miR-205 was significantly down-regulated in gastric cancer cells (all $P < 0.05$). After miR-205 mimic transfection, miR-205 was overexpressed; the relative cellular migration rate of HGC27 cells decreased from $(54.7 \pm 4.1)\%$ to $(34.1 \pm 4.5)\%$ ($P = 0.005$); and the cellular invasion rate decreased from $(52.8 \pm 6.3)\%$ to $(32.2 \pm 4.9)\%$ ($P = 0.001$). Furthermore, after miR-205 was over-expressed, the expression of E-cadherin, β -catenin were up-regulated ($P = 0.002$, $P = 0.003$) and the expression of N-cadherin, vimentin were down-regulated ($P = 0.005$, $P = 0.004$) and the protein expression of Notch and snail were down-regulated ($P = 0.002$, $P = 0.003$). **Conclusion** miR-205 is down-regulated in gastric cancer cells and it is closely related to the invasion and migration of HGC27 cells. The molecular mechanism maybe related to the inhibition of EMT progress and Notch/snail pathway.

Key words: miR-205; EMT; Gastric cancer; Invasion; Migration

摘要: 目的 探讨miR-205对胃癌HGC27细胞侵袭、迁移的作用及其机制。**方法** 实时荧光定量PCR法测定4种不同胃癌细胞(AGS、MKN74、HGC27、SGC7901)中miR-205的表达情况。体外培养的HGC27细胞通过转染miR-205 mimic上调细胞中miR-205的表达, 划痕实验和Transwell实验观察其侵袭和迁移能力; Western blot检测上皮间质转化(epithelial-mesenchymal transition, EMT)进程及相关信号通路的活性。**结果** miR-205在4种胃癌细胞中均呈低表达(均 $P < 0.05$)。过表达miR-205后, HGC27细胞的迁移率由 $(54.7 \pm 4.1)\%$ 降低至 $(34.1 \pm 4.5)\%$ ($P = 0.005$); 细胞的侵袭率由 $(52.8 \pm 6.3)\%$ 降低至 $(32.2 \pm 4.9)\%$ ($P = 0.001$)。此外, 过表达miR-205之后, 胃癌细胞中上皮细胞标志物E-cadherin、 β -catenin蛋白表达显著上升($P = 0.002$, $P = 0.003$), 而间质细胞标志物N-cadherin、vimentin的蛋白表达显著下降($P = 0.005$, $P = 0.004$), Notch和snail的蛋白表达水平也显著降低($P = 0.002$, $P = 0.003$)。**结论** miR-205在胃癌细胞中低表达, 且与胃癌细胞的侵袭和迁移密切相关; 其分子机制可能与抑制EMT及Notch/snail信号通路有关。

关键词: miR-205; 上皮间质转化; 胃癌; 侵袭; 迁移

中图分类号: R735.2 **文献标识码:** A

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0 引言

胃癌作为消化系统的常见恶性肿瘤之一, 发病率及死亡率一直居高不下, 胃癌的侵袭和迁移是患者术后复发及导致患者死亡的主要原因^[1], 故揭示胃癌侵袭和迁移发生的相关分子机制并积极寻找有效的干预靶点对于提高患者的生存率具有十分重要的意义。miR-205定位于1q32.2, 在肿瘤



组织中存在差异性表达,从而发挥抑癌或促癌的作用^[2];据报道miR-205在乳腺癌和卵巢癌中高表达,而在食管癌和胃癌中低表达^[2-5]。且miR-205可靶向VEGFA及FGF2调控乳腺癌化疗耐药^[6];在卵巢癌细胞中,miR-205则靶向TCF21促进细胞侵袭迁移^[7];宫颈癌中,miR-205通过调控IGF-1R影响细胞的增殖及迁移^[8]。由此可见miR-205可通过不同的信号通路及靶基因调控肿瘤细胞的增殖、凋亡、侵袭及迁移等生物学特性,且Xu等^[9]研究显示,在胃癌NCI-H87细胞中,miR-205可能通过靶向ZEB1基因抑制细胞的迁移及EMT进程。考虑到基因调控的复杂性,miR-205对胃癌细胞侵袭迁移的具体作用及分子机制,还需要大量的实验进行验证。本研究拟通过实时荧光定量PCR,初步检测miR-205在几种胃癌细胞中的表达,并通过体外干预miR-205的表达进一步观察其对胃癌细胞HGC27侵袭、迁移能力的影响并探讨其分子机制。

1 材料与方法

1.1 材料与试剂

人胃癌细胞系AGS、MKN74、HGC27、SGC7901及永生化胃黏膜上皮细胞株GES-1均由本实验室自行冻存;胎牛血清(fetal bovine serum, FBS)、RPMI 1640培养液及Opti-MEM培养液购自美国Gibco公司;Transwell小室及Matrigel胶购自美国Corning公司;Lipofectamine²⁰⁰⁰及相关转染试剂购自美国Invitrogen公司;E-cadherin、 β -catenin、N-cadherin、vimentin、Notch、snail及GAPDH抗体购自美国Abcam公司;miR-205 mimic、negative control miR及SYBR Green I real-time PCR kit由上海吉玛制药技术有限公司提供;其余试剂均为国产分析纯。

1.2 实验方法

1.2.1 细胞培养、转染和分组 所有实验用细胞株均常规培养于含10%胎牛血清的RPMI 1640培养液(含100 u/ml青霉素、100 μ g/ml链霉素)中,培养箱条件为37℃、5%CO₂。正常状态下,细胞呈单层贴壁生长,每2天换液一次。待3~5天细胞生长至90%融合后可用胰酶常规消化进行传代。转染:对数生长期的细胞消化后接种于6孔板中,待细胞生长至60%~80%融合,更换为不含血清的培养液,同步化12 h,随后进行转染。实验设置为空白对照组(control)、阴性对照组(negative control miR, miR-NC)、转染组(miRNA-205 mimic, miR-205)。转染方法按说明书进行:将

miR-205或者miR-NC溶解于Opti-MEM培养液中室温孵育5 min,同时另取Lipofectamine²⁰⁰⁰加Opti-MEM培养液室温孵育5 min,然后将两者轻柔混合室温反应20 min。最后将混合物加入到相应组别的细胞中,置于培养箱中孵育6 h后更换为完全培养液继续培养48 h。收集细胞蛋白测定转染效率并进行后续实验分析。

1.2.2 细胞划痕实验 取对数生长期的细胞消化后接种至6孔板中,待细胞长至80%~90%融合时,用10 μ l枪头垂直方向划痕,PBS溶液冲洗细胞两遍后加入培养基,于倒置相差显微镜下观察24 h,每隔10 min拍照记录,观察细胞划痕的修复情况。每组设三个复孔取均值。

1.2.3 Transwell细胞侵袭实验 将各组细胞消化后加不含血清的培养基重悬制成单细胞悬液(密度 2×10^3 个每毫升)。接种细胞于Transwell小室(预先铺好Matrigel胶)上室中,并在下室内加入完全培养液,置于37℃培养箱中培养24 h。取出小室后用PBS冲洗并用棉签轻轻擦除上室内细胞,然后将小室置于90%酒精中固定30 min,加0.1%结晶紫染色10 min,PBS漂洗10 min $\times$ 3次。倒置显微镜下拍照观察并计算染色细胞的个数,每组细胞计数5个视野取均值。

1.2.4 Western blot测定蛋白表达水平 加含有蛋白酶抑制剂的RIPA裂解液提取各组细胞蛋白,并用BCA蛋白定量试剂盒测定蛋白浓度。每组取60 μ g蛋白样品,加4倍体积的上样缓冲液后,95℃加热变性5 min,进行SDS-PAGE凝胶电泳,然后200 mA恒电流将蛋白转移至PVDF膜上。室温下,加5%脱脂奶粉封闭1 h,依据说明书要求加入相应比例的一抗,4℃孵育过夜,复温后TBST洗涤5 min $\times$ 3次。室温下分别加入二抗,继续孵育2 h,TBST洗涤10 min $\times$ 3次。然后于暗房中将ECL发光试剂均匀撒在PVDF膜上激发荧光,压X线片后显影、定影。结果使用ImageJ进行蛋白半定量灰度分析。

1.2.5 实时荧光定量PCR 按照TRIzol说明书要求裂解细胞提取总RNA,测定所提RNA样品的纯度并定量。依据mRNA反转录试剂盒说明书,取2 μ g总RNA合成cDNA,采用SYBR Green I real-time PCR的方法检测mRNA的相对表达量,U6作为内参。引物设计如下:miR-205-F: 5'-GCAATCCTTACTTCCACCG-3', miR-205-R: 5'-GTGCGTGTCGTGGAGTCG-3'; U6-F: 5'-CTCGCTTCGGCAGCACA-3', U6-R: 5'-AACGCTTCACGAATTTGCGT-3'。PCR循环条件为95℃

30 s; 95℃ 5 s, 60℃ 30 s, 40个循环。记录CT值并采用 $2^{-\Delta\Delta CT}$ 法分析mRNA的相对表达量。

1.3 统计学方法

所得数据均采用SPSS13.0统计软件进行分析。实验结果计量资料用均数±标准差($\bar{x}\pm s$)表示。两组计量资料的组间差异采用 t 检验, 多组计量资料行单因素方差分析, 多组计量资料的两两比较采用Bonferroni校正的 t 检验, 计数资料的比较采用 χ^2 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 miR-205在胃癌细胞中低表达

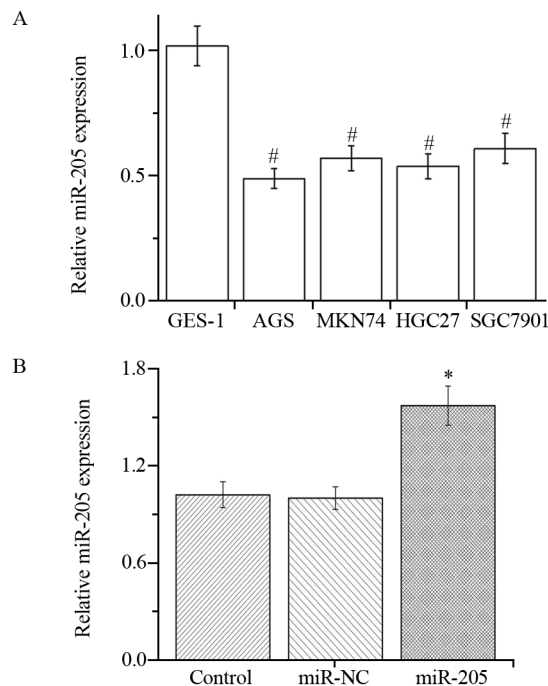
相较于人永生化胃黏膜上皮细胞GES-1中miR-205表达(1.02 ± 0.14), 胃癌细胞系AGS(0.49 ± 0.05)、MKN74(0.64 ± 0.07)、HGC27(0.55 ± 0.06)及SGC7901(0.68 ± 0.08)中miR-205的表达水平均明显降低($P_{AGS}=0.001$, $P_{MKN74}=0.002$, $P_{HGC27}=0.002$, $P_{SGC7901}=0.004$), 见图1A。

2.2 过表达miR-205抑制细胞侵袭迁移

通过脂质体将negative control miR、miR-205 mimic分别转染至HGC27细胞中, 采用qRT-PCR检测miR-205表达水平的变化。结果显示, 转染miR-205 mimic后, miR-205组HGC27细胞中的miR-205表达水平显著升高($P=0.018$), 见图1B。

采用划痕实验测定转染miR-205 mimic后细胞迁移率的变化。结果显示, 划痕后24 h, 转染组细胞迁移率由对照组的(54.7 ± 4.1)%降低至(34.1 ± 4.5)%($P=0.005$), 见图2。

采用Transwell法检测细胞侵袭能力, 发



A: the expression of miR-205 in different gastric cancer cells; B: the expression of miR-205 in HGC27 cells after miR-205 mimic transfection; #: $P<0.05$, compared with GES-1 group; *: $P<0.05$, compared with Control group

图1 qRT-PCR检测胃癌细胞中miR-205的表达水平以及miR-205 mimic的转染效率

Figure1 miR-205 expression in different gastric cancer cells and transfection efficacy of miR-205 mimic detected by qRT-PCR assay

现过表达miR-205后, 转染组细胞侵袭率由对照组的(52.8 ± 6.3)%降低至(32.2 ± 4.9)%($P=0.001$), 见图3。

2.3 过表达miR-205对细胞EMT的影响

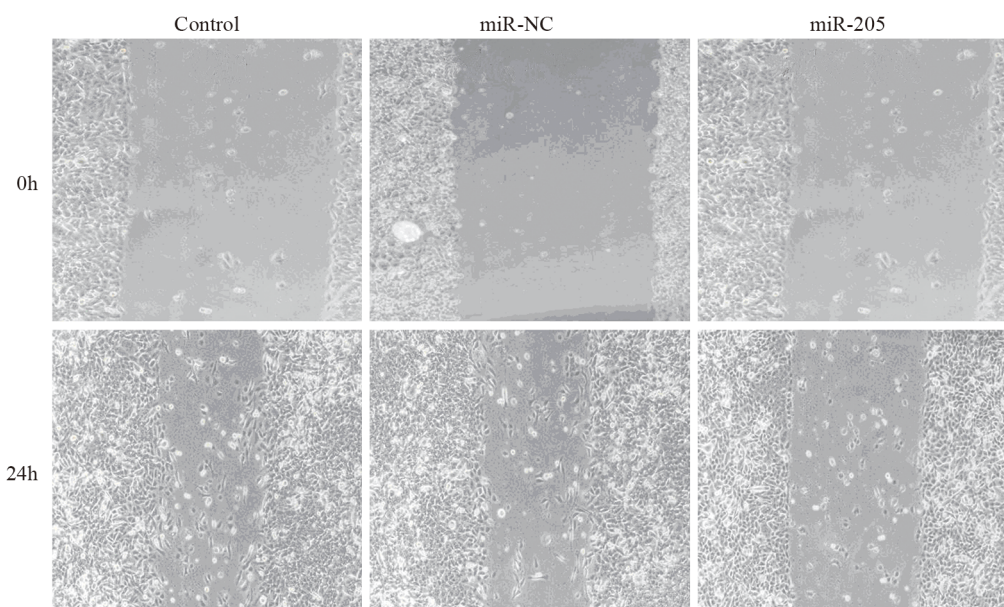


图2 划痕实验检测过表达miR-205对HGC27细胞迁移的影响

Figure2 Effect of miR-205 overexpression on HGC27 cells migration detected by scratch test

为探讨miR-205影响细胞侵袭迁移的可能作用机制,我们通过Western blot检测过表达miR-205对HGC27细胞EMT表达的影响。结果显示,与对照组(E-cadherin (1.01 ± 0.08)、 β -catenin (0.97 ± 0.11)、N-cadherin (1.03 ± 0.09)、vimentin (1.02 ± 0.13))比较,过表达miR-205后上皮细胞标志物E-cadherin (1.82 ± 0.12)及 β -catenin的表达(1.93 ± 0.21)显著升高($P=0.002$, $P=0.003$),而间质细胞标志物N-cadherin (0.54 ± 0.05)及vimentin的表达(0.46 ± 0.06)明显降低($P=0.005$, $P=0.004$),见图4A。

2.4 过表达miR-205对细胞Notch/snail信号通路的影响

与对照组(Notch (1.03 ± 0.11)、snail (0.98 ± 0.13))比较,转染miR-205 mimic后Notch (0.42

± 0.05)和snail的表达(0.37 ± 0.06)明显降低($P=0.002$, $P=0.003$),见图4B。

3 讨论

已有研究证明miR-205在胃癌中发挥抑癌因子样作用,下调miR-205可靶向YY1基因促进胃癌细胞AGS及NCI-N87的增殖^[5];而本实验中实时荧光定量PCR的结果发现,miR-205在不同类型的胃癌细胞中均呈现一定程度的低表达,这与以前的研究结果一致。随后,本实验通过体外细胞实验进一步探讨了miR-205对胃癌细胞HGC27侵袭迁移能力的影响。结果显示,转染miR-205 mimic之后,HGC27细胞的侵袭及迁移能力明显受到抑制。

miRNA的调控作用多是通过相应的靶基因影响相关信号通路,形成复杂的调控网络来实现

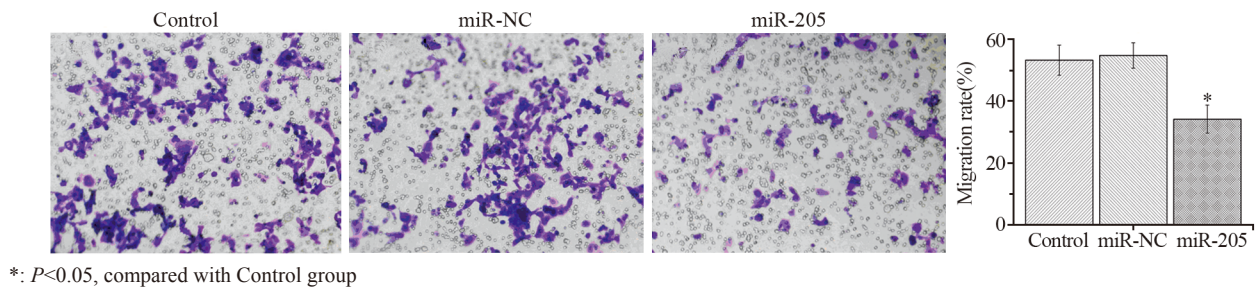
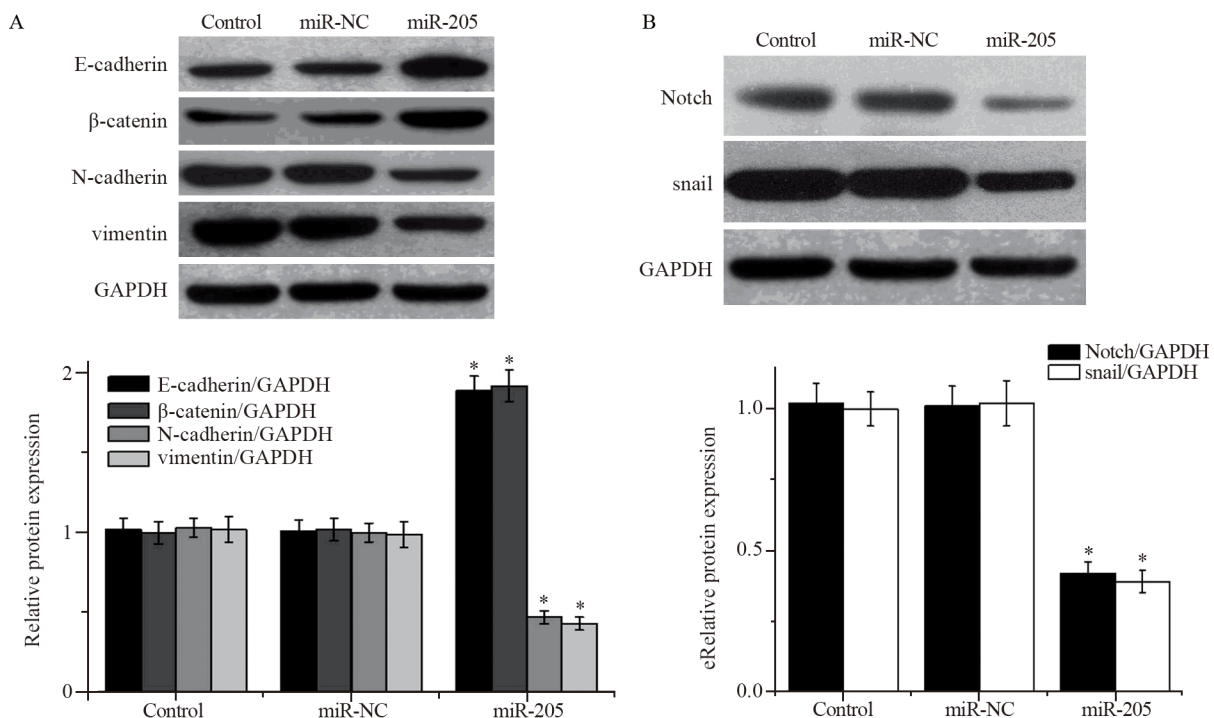


图3 Transwell实验检测过表达miR-205对HGC27细胞侵袭的影响

Figure3 Effect of miR-205 overexpression on HGC27 cells invasion detected by Transwell assay



*: $P<0.05$, compared with Control group

图4 Western blot检测过表达miR-205对HGC27细胞EMT进程及Notch信号通路的影响

Figure4 Effect of miR-205 overexpression on EMT progress and activation of Notch signal pathway in HGC27 cells detected by Western blot

的。在肿瘤细胞侵袭迁移的过程中, 上皮间充质转化是关键的一环, 即在侵袭的过程中癌细胞由上皮细胞形态转化为间质细胞形态, 细胞间的极性丢失且黏附性降低, 同时由于间质细胞结构疏松, 运动能力强, 故而容易迁移^[10-12]。已有大量研究证实miR-205可影响肿瘤细胞的EMT表达^[13-15]。Wang等^[13]在喉鳞状细胞癌SNU899细胞中的研究表明, miR-205可通过影响AKT介导的EMT进程调控细胞的侵袭迁移。曹罗元等^[14]研究显示, miR-205可通过下调ZEB1和ZEB2的表达抑制肾小管HK-2细胞的EMT进程。本研究通过Western blot检测了过表达miR-205对胃癌HGC27细胞中EMT的影响, 结果发现转染miR-205 mimic之后, 上皮细胞标志物E-cadherin及 β -catenin的蛋白表达显著升高而间质细胞标志物N-cadherin及vimentin的蛋白表达明显降低, 说明过表达miR-205后HGC27细胞的EMT被抑制。上皮间充质转化的过程中也涉及到多条信号通路的交互作用, Notch信号通路就是其中一条^[16]。Notch信号通路是一条多调控的复杂通路, 研究显示, Notch信号可通过上调snail、twist、slug、ZEB1及ZEB2等转录因子的表达, 抑制E-cadherin和E-box的结合, 进而上调波形蛋白的表达, 促进细胞EMT的发生^[16-18]。本研究的检测结果发现, 过表达miR-205可抑制Notch/snail信号通路的活性。

综上所述, miR-205在本研究各型胃癌细胞中呈现低表达, 且在胃癌细胞HGC27中上调miR-205可抑制细胞的侵袭迁移; 其分子机制可能与抑制EMT及下调Notch/snail信号通路的活性有关。Notch信号通路及肿瘤细胞EMT均涉及众多复杂的调控机制, miR-205在其中对各种转录因子的具体调控方式还有待进一步深入的研究。

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