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长链非编码 RNA SNHG14/miR-211 对宫颈癌细胞的增殖、侵袭能力的影响 *

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摘要 目的:探讨长链非编码(Long chain non-coding,Lnc)RNA SNHG14/ 微小 RNA(microRNA,miR)-211 对宫颈癌细胞的增殖、侵袭能力的影响。**方法**:宫颈癌细胞株 SiHa 设三组:空白组(不进行转染)、对照组(转染 miR-NC)与 miR-211 组(转染 miR-211 mimic),噻唑蓝[3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di- phenytetrazoliumromide,MTT] 检测细胞增殖活性,Transwell 检测细胞侵袭及转移,实时荧光定量核酸扩增检测系统(Real-time Quantitative PCR, qPCR)检测 LncRNA SNHG14 与 miR-211mRNA 水平,Westem 印迹法检测黏蛋白 4(mucin 4, MUC4)蛋白水平。**结果**:转染后 24 h 与 48 h,miR-211 组的细胞增殖、侵袭、转移指数与 LncRNA SNHG14 与 MUC4 蛋白相对表达水平低于空白组和对照组(P<0.05),miR-211 mRNA 表达水平高于空白组(P<0.05),空白组与对照组对比差异无统计学意义(P>0.05)。**结论**:过表达 miR-211 可抑制 LncRNA SNHG14 的表达,也能抑制 MUC4 表达,从而能抑制宫颈癌细胞的增殖、侵袭及转移。

关键词:miR-211;长链非编码 RNA SNHG14;宫颈癌;细胞增殖;细胞侵袭;黏蛋白 4

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Effects of Long Non-coding RNA SNHG14/miR-211 on the Proliferation and Invasion of Cervical Cancer Cells*

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ABSTRACT Objective: To investigate the effects of long chain non-coding (Lnc) RNA SNHG14/microRNA (miR)-211 on the proliferation and invasion of cervical cancer cells. **Methods:** Cervical cancer cell line SiHa were divided into three groups: blank group (without transfection), control group (transfected with miR-NC) and miR-211 group (transfected with miR-211 mimic), used the MTT to detect cell proliferation activity, Transwell to detect the cell invasion and metastasis, qPCR to detect of LncRNA SNHG14 and miR-211 mRNA levels, Western blotting to detect of of Mucin 4 (MUC4) protein levels. **Results:** At 24 h and 48 h after transfection, the cell proliferation, invasion, metastasis index and the relative expression levels of LncRNA SNHG14 and MUC4 in the miR-211 group were lower than those in the blank group and the control group (P<0.05), and the expression of miR-211 mRNA The level were higher than that of the blank group (P<0.05), and the difference compared between the blank group and the control group were not statistically significant (P>0.05). **Conclusion:** Over-expression of miR-211 can inhibit the expression of LncRNA SNHG14, which can inhibit the expression of MUC4, thereby inhibit the proliferation, invasion and metastasis of cervical cancer cells.

Key words: MiR-211; Long non-coding RNA SNHG14; Cervical cancer; Cell proliferation; Cell invasion; Mucin 4

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前言

宫颈癌是最常见的女性生殖系统恶性肿瘤,也是死亡率居第二位的妇科肿瘤[1]。中晚期宫颈癌患者多死于肿瘤侵袭及转移,导致预后不良[2,3]。无淋巴结转移的早期宫颈癌患者的 5 年生存率在 85 %以上,而伴淋巴结转移的相同临床分期患者,5 年生存率低于 50 %[4]。因此,研究宫颈癌的早期诊断、策略,以促进改善患者的预后一直是我国妇科肿瘤学的重点[5]。微小 RNA(microRNA,miR)是一类非编码 RNA,可与靶 mRNA 的序列互补抑制翻译起始,通过配对的方式结合到相对应的靶基因的 3' 非翻译区,在细胞增殖、侵袭及转移等生物学现象中发挥重要作用[6,7]。miR-211 作为机体组织系统中含量最丰富的 miRNA 之一,可调节数百种靶基因的表达,是一个潜在的肿瘤生物标志,在多种肿瘤组织中的表达水平下降,可发挥促进细

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胞凋亡等作用[8,9]。长链非编码 (Long chain non-coding,Lnc) RNA SNHG14 在调节肿瘤生长过程中扮演重要角色，抑制 LncRNA SNHG14 表达水平可抑制相关恶性肿瘤的迁移与侵袭能力[10,11]。黏蛋白 4(mucin 4, MUC4)是一种高分子量的糖基化蛋白,MUC4 在宫颈癌中 MUC4 的表达量较正常的宫颈组织有明显上升趋势[12,13]。本文具体探讨了 miR-211 介导 LncRNA SNHG14 对宫颈癌细胞的增殖、侵袭能力的影响。现总结报道如下。

1 材料与方法

1.1 主要研究材料

宫颈癌细胞株 SiHa 购置于上海中科院 (在 10 %胎牛血清的 DEME 培养基内,37℃、5 % CO_2 孵箱中培养,培养 2~3 d 后进行传代，取生长状态好、对数生长期的细胞用于实验)，miR-211 mimic 与 miR-NC 购自上海吉玛公司，转染试剂盒购自美国 Sigma 公司,噻唑蓝[3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di- phenytetrazoliumromide,MTT] 检测试剂盒购自上海生工公司,Transwell 小室购自美国 BD 公司，抗 MUC4 抗体、抗 β-actin 抗体够自武汉三鹰公司。

1.2 细胞分组与转染

SiHa 细胞设三组：空白组 (不进行转染)、对照组 (转染 miR-NC)与 miR-211 组(转染 miR-211 mimic)。0.25 %胰酶消化 90 %生长密度的 SiHa 细胞,800 rpm 离心 5 min 后进行悬浮，然后接种到到 6 孔板。培养 24 h 后进行转染,严格按照试剂盒进行操作,转染后 4~6 h 后吸弃 6 孔板培养液,然后进行常规培养。

1.3 噻唑蓝[3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di- phenytetrazoliumromide,MTT] 检测细胞增殖活性

转染后制备出细胞悬液,按照每个孔细胞数为 5×10^3 个进行接种到 96 孔板。培养 24 h 后,每孔加入 MTT 溶液 20 μL,继续培育 4 h。吸弃孔内培养液,添加 DMSO,振荡 10 min,利用酶标仪检测对 490 nm 波长位置进行检测,计算细胞增殖指数。

1.4 Transwell 检测细胞侵袭及转移

转染后制备出细胞悬液，取 200 μL 细胞悬液垂直缓慢加入 Transwell 小室中央,在 24 孔板下室加入常规培养液。培养 24 h 后取出小室并进行固定,用结晶紫溶液染色,镜下计算细胞侵袭及转移指数。

1.5 实时荧光定量核酸扩增检测系统 (Real-time Quantitative PCR, qPCR)检测 LncRNA SNHG14 与 miR-211 mRNA 水平

转染后提取细胞总 RNA,取 1ng RNA 进行反转录反应得到 cDNA，采用 qPCR 方法检测 LncRNA SNHG14 与 miR-211 mRNA 表达水平,LncRNA SNHG14：上游引物 5'-GAATGTGTGTACTGCAAGCA-3'，下游引物 5'-CATTAACCGGAATTCCAGGCTTTGAC-3';miR-211 上游引物 5'-ACGTTATTCCAAGGCTTGGCCG-3'，下游引物 5'-GGTAACCTTCGGACTTAGTCA-3'。

1.6 Western 印迹法检测 MUC4 蛋白水平

转染后提取细胞总蛋白,沸水浴(100℃)变性 5~10 min,蛋白定量上样 20 μg,跑 SDS-PAGE 电泳,转移到硝酸纤维素膜之上，5 %脱脂牛奶室温封闭 2 h，一抗 (抗 MUC4 抗体、抗 β-actin 抗体)4 ℃孵育过夜,洗涤后二抗室温孵育养 1 h,洗涤后采用增强型化学发光试剂盒进行曝光处理，以 β-actin 作为内参,计算 MUC4 蛋白的相对表达量。

1.7 统计学处理

使用 SPSS 22.00 统计软件,计量数据以($\bar{x}\pm s$)表示,两组间对比为采用两独立样本的 t 检验,多组间比较为单因素方差分析,检验水准为 α=0.05。

2 结果

2.1 细胞增殖指数对比

转染后 24 h 与 48 h,miR-211 组的细胞增殖指数低于空白组和对照组(P<0.05),空白组与对照组对比差异无统计学意义(P>0.05),见表 1。

表 1 三组细胞增殖指数对比(%,$\bar{x}\pm s$)

Table 1 Comparison of three groups of cell proliferation indexes (%, $\bar{x}\pm s$)

Groups	n	24 h	48 h
MiR-211 group	3	35.32±2.19*#	42.66±1.59*#
Control group	3	56.87±4.50	67.02±2.75
Blank group	3	57.01±5.01	68.00±3.81

Note: Compared with the control group, *P<0.05; Compared with the blank group, #P<0.05.

2.2 细胞侵袭及转移指数对比

转染后 24 h 与 48 h,miR-211 组的细胞侵袭及转移指数低于空白组和对照组(P<0.05),空白组与对照组对比差异无统计学意义(P>0.05),见表 2。

2.3 LncRNA SNHG14 与 miR-211mRNA 表达水平对比

转染后 24 h 与 48 h,miR-211 组的 miR-211 mRNA 表达水平高于空白组和对照组 (P<0.05),LncRNA SNHG14 表达水平低于空白组和对照组,空白组与对照组对比差异无统计学意义(P>0.05),见表 3。

2.4 MUC4 蛋白表达水平对比

转染后 24 h 与 48 h,miR-211 组的 MUC4 蛋白表达水平低于空白组和对照组(P<0.05),空白组与对照组对比差异无统计学意义(P>0.05),见表 4。

3 讨论

宫颈癌是女性生殖器常见肿瘤之一,虽然当前医学技术提高,但是该病的 5 年生存率提高不明显。因其早期缺少症状,即使有症状也不具有特异性，很多宫颈癌患者就诊时已为晚期，

表 2 三组细胞侵袭及转移指数对比(%,$\bar{x}\pm s$)

Table 2 Comparison of the three groups of cell invasion and metastasis indexes (%, $\bar{x}\pm s$)

Groups	n	Cell invasion indexes		Cell metastasis indexes	
		24 h	48 h	24 h	48 h
MiR-211 group	3	14.20±3.29*#	28.82±2.77*#	15.09±2.47*#	22.84±3.14*#
Control group	3	34.62±2.88	45.01±3.11	36.09±3.14	46.02±4.82
Blank group	3	35.02±3.11	45.67±2.48	35.98±2.77	48.72±5.11

Note: Compared with the control group, *P<0.05; Compared with the blank group, #P<0.05.

表 3 三组 LncRNA SNHG14 与 miR-211mRNA 相对表达水平对比($\bar{x}\pm s$)

Table 3 Comparison of the relative expression levels of three groups of LncRNA SNHG14 and miR-211 mRNA ($\bar{x}\pm s$)

Groups	n	miR-211		SNHG14	
		24 h	48 h	24 h	48 h
MiR-211 group	3	34.20±2.49*#	41.48±3.11*#	0.67±0.13*#	0.71±0.14*#
Control group	3	1.32±0.12	1.35±0.13	4.82±0.32	4.89±0.23
Blank group	3	1.22±0.11	1.32±0.13	5.10±0.21	5.02±0.19

Note: Compared with the control group, *P<0.05; Compared with the blank group, #P<0.05.

表 4 三组 MUC4 蛋白表达水平对比($\bar{x}\pm s$)

Table 4 Comparison of MUC4 protein expression levels in three groups ($\bar{x}\pm s$)

Groups	n	24 h	48 h
MiR-211 group	3	0.84±0.09*#	0.88±0.12*#
Control group	3	5.02±0.11	5.00±0.10
Blank group	3	4.98±0.13	4.87±0.09

Note: Compared with the control group, *P<0.05; Compared with the blank group, #P<0.05.

用常规方法成功治愈的可能性比较低[14]。流行病学调查显示，宫颈癌总的 5 年生存率几乎达到约 70 %，其中无浸润侵袭者达 80 %～90 %，而局部晚期或浸润侵袭者 5 年生存率分别都均在 50 %以下，宫颈癌的浸润侵袭是影响宫颈癌预后的重要因素[15]。miRNA 是一类长度约为 19-23 个核苷酸的非编码单链小 RNA 分子，miRNA 作为生物体生长发育的重要调控基因，存在潜在的致癌或者抑癌作用[16]。一个 miRNA 得靶基因会随着细胞类型得不同而不同，一个 mRNA 受到多个 miRNA 的调控，然后参与器官形成、胚胎发育等多种过程。在宫颈癌中一些 miRNA 高表达而一些 miRNA 低表达，但是只有小部分 miRNAs 生物学功能得到阐明。miR-211 的作用复杂，合成过程中就受多种因子的调控，肿瘤的发生与 miR-211 表达的异常有关[17,18]。本研究显示转染后 24 h 与 48 h，miR-211 组的细胞增殖、侵袭及转移指数低于空白组和对照组。Zhong Y[3]与 Liu H[16]等学者也具有类似结果，表明 miR-211 的过表达能抑制宫颈癌细胞的转移、侵袭与增殖，可为一个潜在的抑癌基因作用靶标，其他相关研究也具有类似结果。具有类似价值。

本研究显示转染后 24 h 与 48 h，miR-211 组的 miR-211 mRNA 表达水平高于空白组和对照组，LncRNA SNHG14 表达水平低于空白组和对照组，表明 miR-211 与 LncRNA SNHG14 可发生互作作用，miR-211 的高表达能抑制 LncRNA SNHG14 的表达。Lv R [19]Peng X [20] 等学者也分析了 miRNA 表达与 LncRNA 表达之间存在相关性。从机制上分析，对于晚期的有远处转移的患者，失去了手术治愈的机会，放化疗的效果也不佳，为此寻找靶向治疗方法也具有重要的意义。肿瘤发生是一个多基因、多步骤的过程，每个 miRNA 可以调控多个靶基因，而特定靶基因也可以同时被多个 miRNA 调节，表明了 miRNA 参与人体生物学功能的复杂性[21]。LncRNA SNHG14 可作为恶性肿瘤的诊断标志物和潜在治疗靶点，其低表达可抑制肿瘤增殖[22]。

宫颈癌高发年龄为 55 岁左右，近年来其发病有年轻化的趋势。目前宫颈癌的发病机理尚未完全了解明确，但是可归因于基因——环境的相互作用，肿瘤的浸润侵袭与相关基因的异常表达有关。本研究显示宫颈鳞状细胞癌组织中 MUC4 表达阳性率随着分化程度降低、临床分期增加、淋巴结的转移而增高；转染后 24 h 与 48 h，miR-211 组的 MUC4 蛋白表达水平低于空白组和对照组，对照组与空白组对比差异无统计学意义，表明 miR-211 的过表达能抑制 MUC4 的表达。Tong R [23]与 Wan S [24] 等学者也表明 LncRNA PTCSC3 与 LncRNARNA FBXL19-AS1 对宫颈癌细胞的生物学行为具有一定的调控作用。从机制上分析，MUC4 包括 2 个 EGF 样结构域、一个跨膜区及一个磷酸化位点，MUC4 高表达也与宫颈癌的预后具有相关性 [25,26]。MUC4 可以调控表皮生长因子受体(epidermal growth factor receptor，EGFR)的表达，从而促进肿瘤细胞的转移和侵袭能力。表皮生长因子(Epidermal Growth Factor，EGF)可以与胞内酪氨酸激酶受体结合后激活其下游的信号通路，从而促进 MUC4 的转录[27-29]。MUC4 可结合肿瘤抑制蛋白形成蛋

白复合物,激活核内 Wnt 通路,从而导致细胞分裂增殖加快,干扰正常细胞周期[30,31]。并且宫颈癌组织的浸润侵袭多伴随有 MUC4F 的阳性表达,宫颈癌的发生发展是在各种高危因素的基础上,因致癌因子利用不同途径导致细胞增生及凋亡失调而促进宫颈癌的发生发展[32,33]。不过肿瘤浸润侵袭的过程非常复杂,包含多个步骤和因素,与宿主和肿瘤细胞的复杂作用有着密切相关。本研究也有一定的不足,miR-211 对 LncRNA SNHG14 的具体作用机制还不明确,且没有进行抑制性表达分析,可能存在研究偏倚,将在后续研究中进一步加大基础研究的深度。

总之,过表达 miR-211 可抑制 LncRNA SNHG14 的表达,也能抑制 MUC4 表达,从而能抑制宫颈癌细胞的增殖、侵袭及转移。

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