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长链非编码 RNA CCAT1 通过调控 miR-181a-5p 促进肺癌细胞增殖和转移的机制

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[摘要] 目的: 研究长链非编码RNA结肠癌相关转录本1(long non-coding RNA colon cancer-associated transcript-1, lncRNA CCAT1)调控miR-181a-5p对肺癌细胞增殖和转移能力的影响, 并探讨其作用机制。方法: 采用qRT-PCR检测CCAT1和miR-181a-5p在肺癌细胞系A549, PC-9和H226及正常人支气管上皮细胞16HBE中的表达水平。采用生物信息学软件和双荧光素酶报告基因检测CCAT1和miR-181a-5p的靶向调控关系; 常规培养CCAT1表达最高的肺癌细胞系, 分为NC组、si-CCAT1组和si-CCAT1+miR-181a-5p inhibitor, 分别进行空白、CCAT1 siRNA和CCAT1 siRNA+miR-181a-5p inhibitor的转染。qRT-PCR检测各组细胞中CCAT1和miR-181a-5p的表达水平; MTS和平板克隆检测CCAT1对各组细胞增殖能力的影响; Transwell检测CCAT1对各组细胞转移能力的影响; 蛋白质印迹法检测各组细胞中MAPK信号通路的活性。结果: 正常人支气管上皮细胞16HBE相比, CCAT1在肺癌细胞系中的表达均增加, miR-181a-5p在肺癌细胞系中的表达均降低。CCAT1在A549细胞中的表达最高。与NC组相比, CCAT1在si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组中表达降低; 与si-CCAT1组相比, CCAT1在si-CCAT1+miR-181a-5p inhibitor组中表达增加; 与NC组相比, miR-181a-5p在si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组中表达增加; 与si-CCAT1组相比, miR-181a-5p在si-CCAT1+miR-181a-5p inhibitor组中表达降低。生物信息学软件和双荧光素酶报告基因结果显示CCAT1与miR-181a-5p有结合位点。与NC组相比, si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组细胞的增殖、转移能力和MAPK信号通路活性降低; 与si-CCAT1组相比, si-CCAT1+miR-181a-5p inhibitor组细胞增殖、转移能力和MAPK信号通路活性增加。结论: CCAT1通过调控miR-181a-5p促进肺癌细胞增殖和转移。CCAT1可能是治疗肺癌的潜在靶点。

[关键词] 肺癌; 长链非编码RNA CCAT1; miR-181a-5p; 增殖; 转移

Long-chain non-coding RNA CCAT1 promotes proliferation and metastasis of lung cancer cells via regulating miR-181a-5p

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Abstract **Objective:** To investigate the effects and mechanism of long non-coding RNA colon cancer-associated

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transcript-1 (ncRNA CCAT1) on the proliferation and metastasis of lung cancer cells by regulating miR-181a-5p. **Methods:** The expression of CCAT1 and miR-181a-5p in lung cancer cell lines A549, PC-9 and H226 and normal human bronchial epithelial cells 16HBE were detected by qRT-PCR. The bioinformatics software and dual luciferase reporter gene were used to detect the targeted regulation of CCAT1 and miR-181a-5p. The lung cancer cell line with the highest CCAT1 expression was routinely cultured, which was divided into NC group, si-CCAT1 group and si-CCAT1+miR-181a-5p inhibitor, cells were transfected with blank, CCAT1 siRNA and CCAT1 siRNA+miR-181a-5p inhibitor, respectively. The expression levels of CCAT1 and miR-181a-5p in each group were detected by qRT-PCR. The effects of CCAT1 on the proliferation of cells in each group were detected by MTS and plate cloning. The effect of CCAT1 on the cell metastasis ability of each group was detected by Transwell. The activity of the MAPK signaling pathway in the cells of the group was detected by Western blotting. **Results:** Compared with 16HBE in normal human bronchial epithelial cells, the expression of CCAT1 was increased in lung cancer cell lines, and the expression of miR-181a-5p was decreased in lung cancer cell lines. CCAT1 has the highest expression in A549 cells. Compared with the NC group, CCAT1 was down-regulated in the si-CCAT1 and si-CCAT1+miR-181a-5p inhibitor groups; compared with the si-CCAT1 group, CCAT1 was increased in the si-CCAT1+miR-181a-5p inhibitor group. compared to the NC group, miR-181a-5p was increased in the si-CCAT1 and si-CCAT1+miR-181a-5p inhibitor groups; compared to the si-CCAT1 group, miR-181a-5p expression was reduced in the si-CCAT1+miR-181a-5p inhibitor group. Bioinformatics software and dual luciferase reporter gene results showed that CCAT1 has a binding site with miR-181a-5p. Compared with the NC group, the proliferation, metastasis and MAPK signaling pathways of the si-CCAT1 and si-CCAT1+miR-181a-5p inhibitor groups were decreased; compared with the si-CCAT1 group, the cell proliferation, metastasis ability and MAPK signaling pathway activity of si-CCAT1+miR-181a-5p inhibitor group were increased. **Conclusion:** CCAT1 promotes the proliferation and metastasis of lung cancer cells by regulating miR-181a-5p. CCAT1 may be a potential target for the treatment of lung cancer.

Keywords lung cancer; long-chain non-coding RNA CCAT1; miR-181a-5p; proliferation; metastasis

肺癌是常见的恶性肿瘤之一, 数据^[1]显示: 美国在2019年约有25万例新发肺癌病例, 占2019年所有新诊断的癌症患者的13%, 肺癌死亡人数约为14万例, 远高于前列腺癌和乳腺癌的人数, 是美国对生命威胁最大的癌症, 而发展中国家面临的情况比发达国家要严峻得多。据文献[2]报道: 每100万中国人中约有78.2例新诊断为肺癌, 2014年共有约63万例左右患者死于肺癌。有研究^[3]指出: 虽然肺癌的治疗取得了一定的进展, 但是患者预后仍然较差, 因此仍需不断的研究肺癌的治疗。长链非编码RNA结肠癌相关转录本1(long non-coding RNA colon cancer-associated transcript-1, lncRNA CCAT1)位于人类染色体8q24.21上, 长度为2 628个碱基对, 少量表达在正常肝组织和小肠组织中, 其他正常组织未见表达, 其导致结肠癌的基因突变, 在结直肠癌中高表达, 是促进结直肠癌进展和预后不良相关的lncRNA^[4]。近年来有研究^[5-7]发现: CCAT1的表达异常与食管癌、胃癌和前列腺癌等的发生发展也密切相关。另有研究

^[8-10]在肺癌中同样发现CCAT1表达异常, 并促进肿瘤增殖、侵袭转移和耐药。本文拟研究lncRNA CCAT1调控miR-181a-5p对肺癌细胞增殖和转移能力的影响, 并探讨其作用机制。

1 材料与方法

1.1 实验试剂

人肺癌细胞系A549, PC-9和H226及正常人支气管上皮细胞16HBE购自美国ATCC细胞库; DMEM-F12, RPMI-1640培养基和FBS购自美国Gibco公司; TRIzol, CCAT1, miR-181a-5p和内参GAPDH引物购自上海生工试剂公司; 反转录试剂盒购自美国Thermo公司; qRT-PCR试剂盒购自德国QIAGEN公司; CCAT1 siRNA, miR-181a-5p inhibitor, miR-181a-5p mimic、野生型(WT)CCAT1和突变型(MUT)CCAT1质粒购于上海吉玛基因公司; MTS试剂购美国Biovision公司; Transwell小室购自美国BD公司; 双荧光素酶报

告基因检测试剂盒、RIPA裂解液和BCA检测蛋白浓度试剂盒购自北京Solarbio公司; MAPK, pMAPK, ERK, pERK, MEK, pMEK和GAPDH抗体购自英国Abcam公司。

1.2 细胞培养

细胞快速复苏后重悬至培养基中, 放置在37℃, 5%CO₂的全湿培养箱中。A549细胞培养基为DMEM-F12; PC-9, H226和16HBE培养基为RPMI-1640, 细胞融合度为95%左右时, 进行传代, 用于后续实验研究。

1.3 qRT-PCR

细胞弃掉培养基后PBS洗涤3次, 加入TRIzol试剂裂解, 采用氯仿和异丙醇试剂提取细胞中总的RNA。并采用反转录试剂盒将其合成cDNA。以cDNA作为扩增模板, 按照qRT-PCR试剂盒说明书, 以95℃ 5s, 40个95℃变性5s, 60℃ 30s循环进行PCR扩增反应。以GAPDH基因为内参, 用2^{-ΔΔC_t}法计算各个目的基因的相对表达量。CCAT1正向引物: 5'-CATTGGGAAAGGTGCCGAGA-3', 反向引物: 5'-ACGCTTAGCCATACAGAGCC-3'; miR-181a-5p正向引物: 5'-ACACTCCAGCTGGGAACATTCAACGCT-GTCGG-3', 反向引物: 5'-TGGTGTCTGTGGAGTCG-3'; GAPDH正向引物: 5'-GGGAGCCAAAAGGGTTCAT-3', 反向引物: 5'-GAGTCCTTCCACGATACCAA-3'。

1.4 双荧光素酶报告基因实验

常规培养CCAT1表达最高的肺癌细胞系, 生长状态较好时以1 000个/孔接种至96孔板内, 分为CCAT1-wt+NC共转染组; CCAT1-wt+miR-181a-5p mimic共转染组; CCAT1-mut+NC共转染组; CCAT1-mut+miR-181a-5p mimic共转染组。细胞贴壁后采用Lip 2000将对应的质粒转入各组细胞中, 转染48 h后, 采用双荧光素酶报告基因试剂盒检测各组细胞荧光素酶活性。

1.5 细胞分组及转染

常规培养CCAT1表达最高的肺癌细胞系, 生长状态较好时以2×10⁵个/孔接种至6孔板内, 分为NC(对照)组、si-CCAT1(CCAT1 siRNA)组、si-CCAT1+miR-181a-5p inhibitor(CCAT1 siRNA+miR-181a-5p inhibitor共转染)组。细胞贴壁后采用Lip 2000将对应的siRNA或inhibitor转入各组细胞中, 放置于37℃, 5%CO₂全湿细胞孵育箱中。转染12 h

后更换新鲜完全培养基继续培养。

1.6 MTS实验检测细胞活性

常规培养CCAT1表达最高的肺癌细胞系, 生长状态较好时以1 000个/孔接种至96孔板内, 分为NC组、si-CCAT1组、si-CCAT1+miR-181a-5p inhibitor组。按上述细胞转染方法将siRNA或inhibitor转入各组细胞中。细胞转染48 h后, 更换100 μL新鲜培养基, 每孔加入20 μL MTS试剂, 设置空白对照孔, 培养箱中孵育2 h, 全波长扫描仪检测490 nm处OD(吸光度)值。细胞增殖率=实验组OD值/对照组OD值。

1.7 平板克隆检测细胞克隆形成能力

常规培养CCAT1表达最高的肺癌细胞系, 生长状态较好时以1 000个/孔接种至6孔板内, 分为NC组、si-CCAT1组、si-CCAT1+miR-181a-5p inhibitor组。按上述细胞转染方法将siRNA或inhibitor转入各组细胞中。形成肉眼可见克隆团时, 终止培养, 用甲醇固定细胞, 苏木精染色, 计数细胞克隆团数目。

1.8 Transwell检测细胞转移能力

取转染48 h的NC组、si-CCAT1组和si-CCAT1+miR-181a-5p inhibitor组细胞, 以2×10⁵个细胞/100 μL无血清培养基加入到Transwell膜上, 放置培养箱中培养12 h后终止培养, 将未转移的细胞洗去后用甲醇固定细胞, 苏木精染色, 在放大倍数为100倍的显微镜下计数5个视野的细胞穿膜数目, 并计算其平均值。

1.9 蛋白质印迹法

收集转染48 h的NC组、si-CCAT1组和si-CCAT1+miR-181a-5p inhibitor组细胞, 用PBS洗后加入RIPA裂解液裂解, 超低速离心获得蛋白上清液, 测得蛋白浓度, 加热煮沸使得蛋白变性, 采用10%的SDS-PAGE进行蛋白分离, 湿转PVDF膜, 室温封闭膜1 h, 用一抗(MAPK, pMAPK, ERK, pERK, MEK和pMEK一抗稀释浓度比为1:500, GAPDH一抗稀释浓度比为1:1 000)4℃孵育过夜, 二抗室温孵育2 h, ECL化学发光法曝光。用Image J软件分析蛋白灰度值。

1.10 统计学处理

采用SPSS 19.0统计学软件进行数据分析。数据均以均数±标准差($\bar{x} \pm s$)表示, *t*检验分析两组间

的差异。方差分析比较多组间的差异, 多组间的两两比较采用Dunnett-*t*检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 肺癌细胞系中CCAT1和miR-181a-5p的表达

qRT-PCR检测人肺癌细胞系A549, PC-9和H226及正常人支气管上皮细胞16HBE中CCAT1和miR-181a-5p的表达情况, 结果显示: CCAT1在肺癌细胞中的表达显著高于正常人支气管上皮细胞, 在A549细胞中表达最高($P<0.05$), 选择A549细胞进行后续实验。miR-181a-5p在肺癌细胞中的表达显著低于正常人支气管上皮细胞($P<0.05$, 图1)。

2.2 各组细胞中CCAT1和miR-181a-5p的表达

收集转染 48 h 的各组A549细胞, qRT-PCR

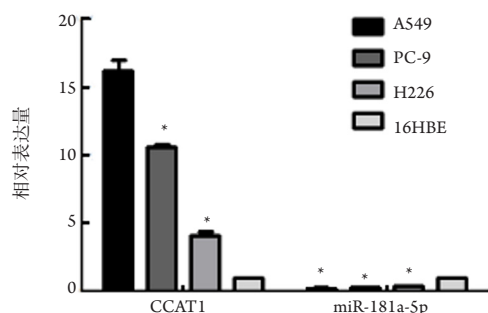


图1 CCAT1和miR-181a-5p在肺癌细胞系中的表达水平

Figure 1 Expression levels of CCAT1 and miR-181a-5p in lung cancer cell lines

与16HBE比较, $*P<0.05$ 。

Compared to 16HBE, $*P<0.05$.

结果显示: 与NC组相比, CCAT1在si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组中表达降低($P<0.05$); 与si-CCAT1组相比, CCAT1在si-CCAT1+miR-181a-5p inhibitor组中表达增加($P<0.05$), 表明CCAT1 siRNA可以干扰A549细胞中CCAT1的表达, 抑制miR-181a-5p的表达可以增加CCAT1的表达。与NC组相比, miR-181a-5p在si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组中表达增加($P<0.05$); 与si-CCAT1组相比, miR-181a-5p在si-CCAT1+miR-181a-5p inhibitor组中表达降低($P<0.05$), 表明miR-181a-5p inhibitor可以抑制A549

细胞中miR-181a-5p的表达, 抑制CCAT1的表达可以增加miR-181a-5p的表达(图2)。

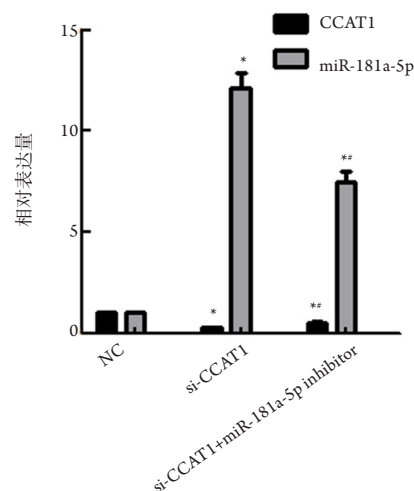


图2 CCAT1和miR-181a-5p在各组细胞中的表达

Figure 2 Expression of CCAT1 and miR-181a-5p in cells of each group

与NC组比较, $*P<0.05$; 与si-CCAT1组比较, $*P<0.05$ 。

Compared to the NC group, $*P<0.05$; Compared to the si-CCAT1 group, $*P<0.05$.

2.3 CCAT1对miR-181a-5p表达的调控作用

采用StarBase v2.0生物信息学软件进行预测, 结果显示: miR-181a-5p是CCAT1的靶基因, 两者预测结合序列如图3A所示。双荧光素酶报告基因结果显示: 与CCAT1-wt+NC共转染组相比, CCAT1-wt+miR-181a-5p mimic共转染组的荧光素酶活性显著降低($P<0.05$), 而CCAT1-mut+NC与CCAT1-mut+miR-181a-5p mimic共转染组之间的荧光素酶活性无显著差异($P>0.05$, 图3B)。

2.4 CCAT1调控miR-181a-5p对肺癌细胞增殖能力的影响

采用MTS实验(图4A)和平板克隆实验(图4B, 4C)检测细胞增殖能力, 结果显示: 与NC组相比, si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组细胞增殖能力降低($P<0.05$); 与si-CCAT1组相比, si-CCAT1+miR-181a-5p inhibitor组细胞增殖能力增加($P<0.05$)。表明干扰CCAT1的表达通过调控miR-181a-5p抑制A549细胞的增殖能力。

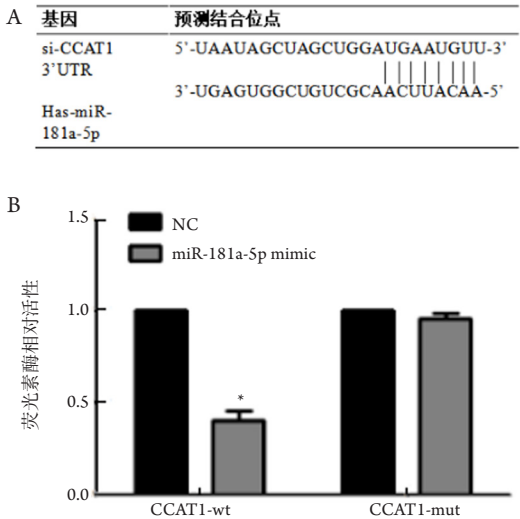


图3 CCAT1对miR-181a-5p表达的调控作用

Figure 3 CCAT1 regulates miR-181a-5p expression

(A)StarBase v2.0生物信息学软件预测CCAT1和miR-181a-5p的结合位点; (B)双荧光素酶报告基因实验。与NC组比较, * $P<0.05$ 。

(A) StarBase v2.0 bioinformatics software predicts the binding sites of CCAT1 and miR-181a-5p; (B) Double luciferase reporter gene experiment. Compared with the NC group, * $P<0.05$.

2.5 CCAT1调控miR-181a-5p对肺癌细胞转移能力的影响

Transwell实验检测细胞转移能力, 结果显示: 与NC组相比, si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组细胞转移能力降低($P<0.05$); 与si-CCAT1组相比, si-CCAT1+miR-181a-5p inhibitor组细胞转移能力增加($P<0.05$, 图5)。表明干扰CCAT1的表达通过调控miR-181a-5p抑制A549细胞的转移能力。

2.6 CCAT1调控miR-181a-5p对肺癌细胞MAPK信号通路活性的影响

蛋白质印迹法结果(图6)示: 与NC组相比, si-CCAT1和si-CCAT1+miR-181a-5p inhibitor组细胞中MAPK, ERK和MEK表达无明显变化, pMAPK, pERK和pMEK的蛋白表达降低($P<0.05$); 与si-CCAT1组相比, si-CCAT1+miR-181a-5p inhibitor组细胞中MAPK, ERK和MEK表达无明显变化, pMAPK, pERK和pMEK的蛋白表达增加($P<0.05$)。表明干扰CCAT1的表达通过调控miR-181a-5p抑制A549细胞中MAPK信号通路活性。

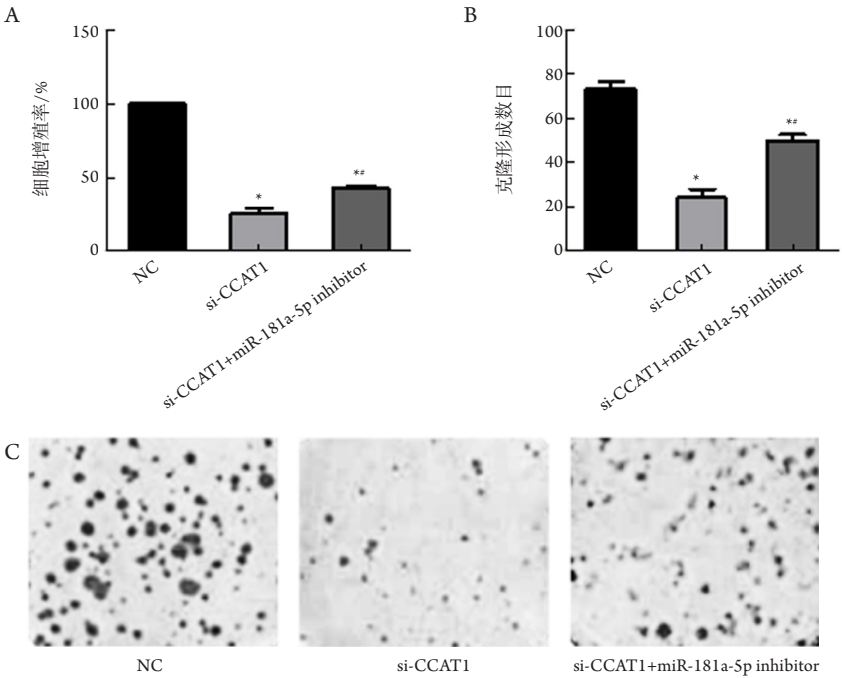


图4 CCAT1调控miR-181a-5p对肺癌细胞增殖能力的影响

Figure 4 Effect of CCAT1 regulation of miR-181a-5p on lung cancer cell proliferation ability

(A)细胞增殖柱状图; (B)平板克隆柱状图; (C)平板克隆(HE染色, $\times 200$)。与NC组比较, * $P<0.05$; 与si-CCAT1组比较, ** $P<0.05$ 。

(A) Histogram of cell proliferation; (B) Histogram of plate clone; (C) Plate clone (HE, $\times 200$). Compared to the NC group, * $P<0.05$; Compared to the si-CCAT1 group, ** $P<0.05$.

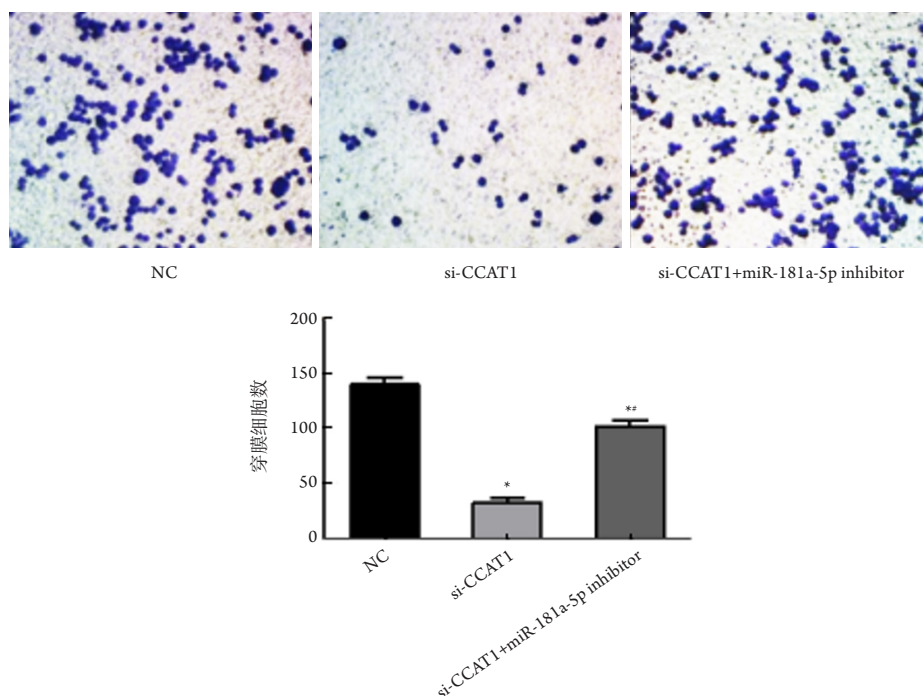


图5 CCAT1调控miR-181a-5p对肺癌细胞转移能力的影响(HE, $\times 200$)

Figure 5 Effect of CCAT1 regulation of miR-181a-5p on lung cancer cell metastatic capacity (HE, $\times 200$)

与NC组比较, $*P<0.05$; 与si-CCAT1组比较, $*P<0.05$ 。

Compared to the NC group, $*P<0.05$; Compared to the si-CCAT1 group, $*P<0.05$.

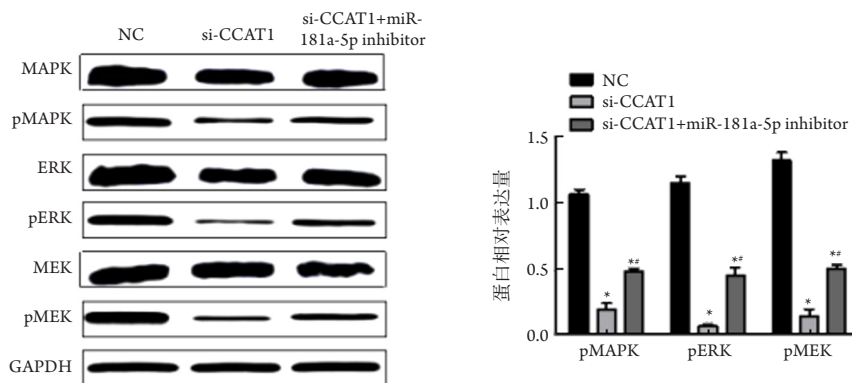


图6 CCAT1调控miR-181a-5p对MAPK信号通路活性的影响

Figure 6 Effect of CCAT1 regulation of miR-181a-5p on MAPK signaling pathway activity

与NC组比较, $*P<0.05$; 与si-CCAT1组比较, $*P<0.05$ 。

Compared to the NC group, $*P<0.05$; Compared to the si-CCAT1 group, $*P<0.05$.

3 讨论

肺癌是全球性的公共卫生问题,是癌症相关死亡的主要原因,且近几年来其发病率和病死率仍高居不下^[1]。手术切除、化学疗法和放射治疗等传统治疗方法仍是肺癌治疗的主要手段,近年来分子靶向治疗和生物免疫治疗等新型治疗方法也在肺癌治疗中取得了长足的进步,但是晚期患者

手术切除的局限性以及化疗、放疗和分子靶向治疗的耐药性,导致患者的5年生存率仍然很低^[3]。而目前肺癌的发病机制尚未完全明确,流行病学研究^[11]表明:吸烟、饮酒、遗传因素、环境空气污染、饮食和肥胖等是肺癌发病的高危因素,可能参与肺癌的发病机制。另外一项研究^[12]表明家族肿瘤病史增加了肺癌的易感性。因此在基因分子水平深入研究肺癌的发病机制可能为肺癌的治

疗提供新靶点。

LncRNA是一大类各种各样的转录RNA分子,通常长度超过200个核苷酸,其蛋白质编码能力有限。有研究^[13]揭示了lncRNA在人类疾病中的关键作用,包括癌症、心血管疾病和内分泌代谢疾病等常见威胁人们生命健康的疾病。改变lncRNA的表达可以抑制肿瘤发生、生长和转移等多种生物学过程,可作为抗肿瘤治疗靶点^[14]。据文献[5]报道:结肠癌相关lncRNA CCAT1在多种肿瘤中发挥癌基因的功能,在食管癌细胞系中CCAT1的表达与耐药性呈正相关,CCAT1敲低在体内和体外均抑制细胞增殖和顺铂的耐药性。研究^[6]表明:CCAT1在胃癌组织和细胞系中表达增加,干扰CCAT1的表达胃癌细胞增殖和侵袭能力减少,细胞凋亡增加。同时有研究^[8]报道:CCAT1在肺腺癌组织中表达的增加,并能够通过诱导上皮间质转化过程促进肺腺癌细胞的侵袭和转移。Xu等^[9]发现CCAT1/Let-7c/Wnt通过调控轴来调控肺癌干细胞的分裂。并有研究^[10]表明CCAT1增加促进非小细胞肺癌细胞对顺铂的抗性。CCAT1可能是治疗肺癌的潜在靶点。尽管lncRNAs缺乏功能蛋白的编码能力,但它们可能与其他重要元素结合,从而调节人类癌症的生物学或病理过程, RNA转录物调控机制包括作为miRNA竞争内源性RNA(ceRNA)发挥作用。Sui等^[15]在肺癌领域进行了计算分析,并确定了人肺鳞状细胞癌中lncRNA之间的海绵相互作用网络。

研究^[10]表明:在非小细胞肺癌中,CCAT1直接与miR-130a-3p相互作用,负调控miR-130a-3p的表达发挥耐药功能。而研究^[7,16]报道:在宫颈癌和子宫内膜癌中,CCAT1均通过负调控miR-181a-5p促进肿瘤细胞增殖、侵袭和转移。本文采用qRT-PCR,发现在肺癌细胞系中CCAT1的表达增加,而miR-181a-5p的表达减少;且抑制miR-181a-5p的表达可以增加肺癌细胞中CCAT1的表达,抑制CCAT1的表达可以增加肺癌细胞中miR-181a-5p的表达。进一步双荧光素酶报告基因实验显示:CCAT1靶向调控miR-181a-5p,表明在肺癌中CCAT1充当miR-181a-5p的ceRNA。有研究^[17]指出:miR-181a-5p表达异常导致肿瘤发生发展,其在非小细胞肺癌组织和细胞系中表达降低,转染miR-181a-5p的模拟物后A549细胞的增殖和迁移受到抑制,miR-181a-5p在非小细胞肺癌中充当抑癌因子。本研究生物学功能实验结果显示:干扰CCAT1的表达通过调控miR-181a-5p抑制肺癌细胞的增殖和转移能力;且蛋白质印迹法结果示干扰

CCAT1的表达通过调控miR-181a-5p抑制肺癌细胞中MAPK信号通路的活性。有学者^[18]认为MAPK信号通路是调控肿瘤增殖和转移的重要途径之一,在肺癌中处于激活状态。据报道^[19-20],CCAT1在髓母细胞瘤和甲状腺癌中通过激活MAPK信号通路促进肿瘤细胞的增殖、迁移和侵袭。因此,在肺癌中CCAT1充当miR-181a-5p的ceRNA通过激活MAPK信号通路增强肿瘤细胞的增殖和转移能力。

综上,本研究发现了CCAT1在肺癌中新的调控机制,即CCAT1/miR-181a-5p轴可能通过调控MAPK信号转导来促进细胞增殖和转移,为CCAT1成为肺癌治疗靶标进一步提供了实验室依据。

参考文献

1. Siegel RL, Miller KD. Cancer statistics, 2019[J]. CA Cancer J Clin, 2019, 69(1): 7-34.
2. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014[J]. Chin J Cancer Res, 2018, 30(1): 1-12.
3. 向勇. 肺恶性肿瘤的高危因素、治疗及预后[J]. 世界最新医学信息文摘, 2019, 19(65): 243.
4. XIANG Yong. High-risk factors, treatment and prognosis of lung malignancies[J]. World Latest Medicine Information, 2019, 19(65): 243.
5. Guo X. CCAT1: an oncogenic long noncoding RNA in human cancers[J]. J Cancer Res Clin Oncol, 2017, 143(4): 555-562.
6. Hu M, Zhang Q, Tian XH, et al. lncRNA CCAT1 is a biomarker for the proliferation and drug resistance of esophageal cancer via the miR-143/PLK1/BUBR1 axis[J]. Mol Carcinog, 2019, 1(1): 1-9.
7. Li Y, Zhu G, Ma Y. lncRNA CCAT1 contributes to the growth and invasion of gastric cancer via targeting miR-219-1[J]. J Cell Biochem, 2019, 120(12): 19457-19468.
8. Shen H, Wang L, Xiong J, et al. Long non-coding RNA CCAT1 promotes cervical cancer cell proliferation and invasion by regulating the miR-181a-5p/MMP14 axis[J]. Cell Cycle, 2019, 18(10): 1110-1121.
9. Lin H, Cheng W, Yan H. Overexpression of the long noncoding RNA CCAT1 promotes metastasis via epithelial-to-mesenchymal transition in lung adenocarcinoma[J]. Oncol Lett, 2018, 16(2): 1809-1814.
10. Xu C, Xiao G, Zhang B, et al. CCAT1 stimulation of the symmetric division of NSCLC stem cells through activation of the Wnt signalling cascade[J]. Gene Ther, 2018, 25(1): 4-12.
11. Hu B, Zhang H, Wang Z, et al. lncRNA CCAT1/miR-130a-3p axis increases cisplatin resistance in non-small-cell lung cancer cell line by targeting SOX4[J]. Cancer Biol Ther, 2017, 18(12): 974-983.
12. 马书梅, 刘瑞娟, 张影影. 肺癌的流行病学[J]. 世界最新医学信

- 息文摘, 2019, 19(26): 77-78.
- MA Shumei, LIU Ruijuan, ZHANG Yingying. The epidemiology of lung cancer[J]. World Latest Medicine Information, 2019, 19(26): 77-78.
12. Yoshida K, Takizawa Y, Nishino Y, et al. Association between Family History of Cancer and Lung Cancer Risk among Japanese Men and Women[J]. Tohoku J Exp Med, 2019, 247(2): 99-110.
 13. Knoll M, Lodish HF. Long non-coding RNAs as regulators of the endocrine system[J]. Nat Rev Endocrinol, 2015, 11(3): 151-160.
 14. 申娟. LncRNA在肺癌中的表达及调控机制研究[D]. 南京: 东南大学, 2017.
 - SHEN Xian. Study on the expression and regulation mechanism of lncRNA in lung cancer[D]. Nanjing: Southeast University, 2017.
 15. Sui J, Xu SY, Han J, et al. Integrated analysis of competing endogenous RNA network revealing lncRNAs as potential prognostic biomarkers in human lung squamous cell carcinoma[J]. Oncotarget, 2017, 8(39): 65997-66018.
 16. Yu J, Jiang L, Gao Y, et al. LncRNA CCAT1 negatively regulates miR-181a-5p to promote endometrial carcinoma cell proliferation and migration[J]. Exp Ther Med, 2019, 17(5): 4259-4266.
 17. Cao Y, Zhao D, Li P, et al. MicroRNA-181a-5p Impedes IL-17-Induced Nonsmall Cell Lung Cancer Proliferation and Migration through Targeting VCAM-1[J]. Cell Physiol Biochem, 2017, 42(1): 346-356.
 18. 许晶. 不可逆性EGFR-TKIs在非小细胞肺癌中获得性耐药机制的体外研究[D]. 北京: 北京市结核病胸部肿瘤研究所, 2018.
 - XU Jing. An in-vitro Study of Acquired Resistance to Irreversible EGFR-TKIs in Non-small Cell Lung Cancer[J]. Beijing: Beijing Tuberculosis Thoracic Tumor Institute, 2018.
 19. Gao R, Zhang R, Zhang C, et al. Long noncoding RNA CCAT1 promotes cell proliferation and metastasis in human medulloblastoma via MAPK pathway[J]. Tumori, 2018, 104(1): 43-50.
 20. Yang T, Zhai H, Yan R, et al. LncRNA CCAT1 promotes cell proliferation, migration, and invasion by down-regulation of miR-143 in FTC-133 thyroid carcinoma cell line[J]. Braz J Med Biol Res, 2018, 51(6): e7046.

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