·论著·

# lncRNA SOX2-OT通过靶向调控miR-452-5p影响宫颈癌细胞增殖、迁移和侵袭

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**摘要 目的** 探讨lncRNA SOX2-OT靶向调控miR-452-5p对宫颈癌细胞增殖、迁移和侵袭的影响。**方法** 将宫颈癌细胞分为对照组、si-NC组、si-SOX2-OT组、si-SOX2-OT+anti-NC组、si-SOX2-OT+anti-miR-452-5p组。检测宫颈癌组织和细胞中lncRNA SOX2-OT、miR-452-5p水平;检测细胞增殖、迁移、侵袭以及相关蛋白表达;观察移植瘤生长情况,检测瘤组织中lncRNA SOX2-OT、miR-452-5p水平。**结果** 在宫颈癌组织和宫颈癌细胞系HeLa、SiHa中,lncRNA SOX2-OT高表达,miR-452-5p低表达($P < 0.05$)。lncRNA SOX2-OT与miR-452-5p间存在靶向关系。与si-NC组比较,si-SOX2-OT组lncRNA SOX2-OT水平、EdU阳性率、迁移细胞数、侵袭细胞数以及PCNA、cyclin D1、MMP-9表达水平降低,miR-452-5p水平和TIMP-2表达水平升高($P < 0.05$)。沉默miR-452-5p可部分逆转沉默lncRNA SOX2-OT对宫颈癌细胞增殖、迁移和侵袭的抑制作用。裸鼠移植瘤实验发现,与si-NC组比较,si-SOX2-OT组移植瘤生长缓慢,体积减小,质量减轻,lncRNA SOX2-OT水平降低,miR-452-5p水平升高($P < 0.05$)。**结论** lncRNA SOX2-OT可促进宫颈癌细胞增殖、迁移和侵袭,与靶向抑制miR-452-5p相关。

**关键词** lncRNA SOX2-OT;miR-452-5p;宫颈癌;增殖;迁移;侵袭
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## Effects of lncRNA SOX2-OT on the proliferation, migration, and invasion of cervical cancer cells through targeted regulation of miR-452-5p

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**Abstract Objective** To explore the effects of long noncoding RNA (lncRNA) SOX2-OT on the proliferation, migration, and invasion of cervical cancer cells through targeted regulation of miR-452-5p. **Methods** Cervical cancer cells were assigned to the control, si-NC, si-SOX2-OT, si-SOX2-OT+anti-NC, and si-SOX2-OT+anti-miR-452-5p groups. lncRNA SOX2-OT and miR-452-5p levels in cervical cancer tissues and cells were measured. Cell proliferation, migration, and invasion, as well as related protein expressions were detected. Transplanted tumor growth was monitored, and lncRNA SOX2-OT and miR-452-5p levels in the tumor tissues were quantified. **Results** lncRNA SOX2-OT was highly expressed and miR-452-5p was lowly expressed in cervical cancer tissues as well as in cervical cancer cell lines HeLa and SiHa ($P < 0.05$). A targeting relationship existed between lncRNA SOX2-OT and miR-452-5p. Compared with the si-NC group, lncRNA SOX2-OT level; EdU positivite rate; migrating cell numbers; invading cell numbers; and PCNA, cyclin D1, and MMP-9 levels were decreased in the si-SOX2-OT group, whereas miR-452-5p and TIMP-2 levels were increased ($P < 0.05$). Notably, miR-452-5p silencing partially reversed the inhibitory effect of silencing lncRNA SOX2-OT on the proliferation, migration, and invasion of cervical cancer cells. The nude mouse xenograft tumor model revealed that, compared with the si-NC group, the tumor growth, volume, and weight, as well as lncRNA SOX2-OT level were decreased in the si-SOX2-OT group, whereas the miR-452-5p level was increased ($P < 0.05$). **Conclusion** lncRNA SOX2-OT promotes the proliferation, migration, and invasion of cervical cancer cells, which may be associated with targeted miR-452-5p inhibition.

**Keywords** lncRNA SOX2-OT; miR-452-5p; cervical cancer; proliferation; migration; invasion

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宫颈癌是全球最常见的女性癌症之一，发病率和死亡率高，且近年来发病呈上升、年轻化趋势，严重威胁女性的身心健康[1]。由于慢性人乳头瘤病毒（human papillomavirus，HPV）感染和清除失败是宫颈癌发生的主要可预防原因，通过早期筛查和预防HPV，结合手术和放疗、化疗等，可显著提高宫颈癌患者的生存率。然而，大部分患者在确诊时已为中晚期，同时受本身异质性和治疗耐药性等因素影响，宫颈癌患者5年生存率极低[2]。尽早预防和及时治疗，寻求新型高效治疗策略，对于治疗宫颈癌至关重要。长链非编码RNA（long noncoding RNA，lncRNA）和微RNA（microRNA，miRNA）为常见的非编码RNA，在多种疾病的发展进程中发挥重要作用。研究[3]发现，lncRNA SRY盒转录因子2重叠转录本（SRY-box transcription factor 2 overlapping transcript，SOX2-OT）高表达可促进三阴性乳腺癌的迁移和转移。miR-452-5p在宫颈癌组织中的表达下调，其过表达可抑制宫颈癌细胞的增殖、迁移和侵袭，抑制体内肿瘤生长[4]。本研究利用starBase网站预测发现lncRNA SOX2-OT与miR-452-5p间存在靶向关系，通过探究lncRNA SOX2-OT靶向调控miR-452-5p对宫颈癌发生和发展的影响，寻求宫颈癌治疗的新靶点。

## 1　材料与方法

### 1.1　材料

1.1.1　标本来源：收集2023年1月至6月间我院收治的20例宫颈癌患者的癌组织和癌旁组织。所有病例经病理检查证实为宫颈癌，且均为初次诊断，未接受过放化疗等治疗。本研究获得我院科研伦理委员会审批[2022年（科研）第107号]，所有患者及其家属知情同意。

1.1.2　细胞和实验动物：人正常宫颈上皮细胞系HUCEC和宫颈癌细胞系HeLa、SiHa，购自深圳市豪地华拓生物科技有限公司；4周龄BALB/c裸鼠，购自海南绍君生物科技有限公司，生产许可证号为SCXK（琼）2023-0009。饲养条件：湿度55%~65%，温度（25 ± 2）℃，12 h光暗交替，自由摄食饮水。本研究获得海南绍君生物科技有限公司实验动物伦理委员会批准（2024-06-105）。

1.1.3　主要试剂和仪器：si-NC、si-SOX2-OT、si-SOX2-OT+anti-NC、si-SOX2-OT+anti-miR-452-5p、miR-NC、miR-452-5p mimics质粒合成和引物设计，均由北京海创科业生物科技有限责任公司完成；增殖细胞核抗原（proliferating cell nuclear antigen，PCNA）、$G_1$/S特异性周期蛋白D1（cyclin D1）抗体，购自武汉博欧特生物科技有限公司；基质金属蛋白酶9（matrix metalloproteinase 9，MMP-9）抗体，购自沈阳万类生物科技有限公司；基质金属蛋白酶组织抑制因子2（tissue inhibitor of metalloproteinases 2，TIMP-2）抗体，购自武汉菲恩生物科技有限公司。光学显微镜，购自北京亿诚恒达科技有限公司；全新凝胶成像系统，购自伯乐生命医学产品（上海）有限公司。

### 1.2　方法

1.2.1　细胞培养：将HUCEC细胞、HeLa细胞、SiHa细胞在37 ℃、5% $CO_2$、湿度饱和环境下的DMEM培养基（含10%胎牛血清和1%青链霉素）中传代培养，选择第3代对数期细胞进行后续实验。

1.2.2　实时定量PCR：提取组织和细胞总RNA，反转录成cDNA，以其为模板进行PCR扩增，应用$2^{-\Delta\Delta Ct}$法计算lncRNA SOX2-OT（*GAPDH*为内参基因）、miR-452-5p（*U6*为内参基因）相对表达水平。引物序列：lncRNA SOX2-OT，正向5'-GTTCATGGCCTGGACTCTCC-3'，反向5'-ATTGCTAGCCCTCACACCTC-3'；*GAPDH*，正向5'-GGTCTCCTCTGACTTCAACA-3'，反向5'-GTGAGGGTCTCTCTCTTCCT-3'；miR-452-5p，正向5'-AAGAGGGCATGGAAACACTG-3'，反向5'-ACTCACCCCATTCTTCAAGG-3'；*U6*，正向5'-GCTTCGGCAGCACATATACTAAAAT-3'，反向5'-CGCTTCACGAATTTGCGTGTCAT-3'。

1.2.3　双萤光素酶报告基因实验：通过starBase网站（http://rnasysu.com/encori/index.php）预测lncRNA SOX2-OT与miR-452-5p间存在结合位点，采用双萤光素酶实验验证两者间是否存在靶向调控关系。将miR-NC和miR-452-5p mimics质粒与构建的SOX2-OT-WT、SOX2-OT-MUT载体分别共转染至HeLa细胞48 h，具体操作参照双萤光素酶试剂盒说明书。根据萤火虫萤光素酶/海肾萤光素酶荧光比值，分析lncRNA SOX2-OT萤光素酶活性变化。

1.2.4　分组和处理：将HeLa细胞分为对照组、si-NC组（转染si-NC质粒48 h）、si-SOX2-OT组（转染si-SOX2-OT质粒48 h）、si-SOX2-OT+anti-NC组（转染si-SOX2-

OT、anti-NC质粒48 h)、si-SOX2-OT+anti-miR-452-5p组(转染si-SOX2-OT、anti-miR-452-5p质粒48 h),转染均采用lipofectamine 2000。

1.2.5　EdU实验:收集分组处理后的细胞,清洗后用甲醛固定,依次进行EdU、DAPI室温避光染色,荧光显微镜下观察,分析EdU阳性率。

1.2.6　Transwell实验:迁移实验,收集分组处理后的细胞,制成单细胞悬液,加入上室,下室同时加入DMEM培养基(含10%胎牛血清),在37 ℃下共培养24 h,取出小室,固定染色,光学显微镜下观察、计数。侵袭实验在迁移实验基础上,上室加入Matrigel凝胶,其余操作相同。

1.2.7　Western blotting:用蛋白裂解液提取分组处理后细胞的蛋白,BCA定量,将蛋白沸水浴变性,SDS-PAGE分离,转入PVDF膜后用脱脂奶粉封闭1 h,4 ℃下与PCNA、cyclin D1、MMP-9、TIMP-2一抗孵育过夜,室温下与二抗反应1 h。增强型化学发光试剂显影后,收集图像,进行蛋白灰度分析。

1.2.8　裸鼠移植瘤实验:裸鼠适应性喂养1周后,分别在裸鼠右前肢腋下皮下注射0.2 mL转染si-NC、si-SOX2-OT质粒的HeLa细胞悬液($5 \times 10^6$/200 μL)。每天观察裸鼠状态,5 d测量1次肿瘤体积,35 d后处死裸鼠,取瘤组织称重。取部分瘤组织,检测lncRNA SOX2-OT、miR-452-5p水平。剩余瘤组织用甲醛固定,浸蜡,制成石蜡切片,脱蜡至水后进行HE染色,光学显微镜下观察瘤组织的病理形态。

1.3　统计学分析

采用SPSS 25.0软件进行统计分析。符合正态分布的计量资料以$\bar{x} \pm s$表示,2组间比较采用$t$检验,多组间比较采用单因素方差分析,组间两两比较采用SNK-$q$检验。$P < 0.05$为差异有统计学意义。

## 2　结果

2.1　宫颈癌组织和细胞中lncRNA SOX2-OT、miR-452-5p水平

与癌旁组织比较,宫颈癌组织中lncRNA SOX2-OT水平升高,miR-452-5p水平降低($P < 0.05$);与HUCEC细胞比较,HeLa和SiHa细胞中lncRNA SOX2-OT水平升高,miR-452-5p水平降低($P < 0.05$)。见表1。HeLa细胞更具代表性,用于后续实验。

表1　宫颈癌组织和细胞中lncRNA SOX2-OT、miR-452-5p水平比较

Tab.1　Comparison of lncRNA SOX2-OT and miR-452-5p levels in cervical cancer tissues and cells

| Item | $n$ | lncRNA SOX2-OT | miR-452-5p |
|---|---|---|---|
| Tissue | | | |
| Adjacent normal tissue | 20 | 0.53 ± 0.08 | 0.90 ± 0.11 |
| Cervical cancer tissue | 20 | 0.94 ± 0.16[1)] | 0.49 ± 0.07[1)] |
| Cell | | | |
| HUCEC | 6 | 0.42 ± 0.05 | 0.93 ± 0.14 |
| HeLa | 6 | 0.91 ± 0.12[2)] | 0.47 ± 0.06[2)] |
| SiHa | 6 | 0.88 ± 0.10[2)] | 0.50 ± 0.09[2)] |

1) $P < 0.05$ vs. adjacent normal tissue; 2) $P < 0.05$ vs. HUCEC cells.

2.2　lncRNA SOX2-OT与miR-452-5p的靶向关系

starBase网站预测结果显示,lncRNA SOX2-OT与miR-452-5p间存在结合位点。见图1。SOX2-OT-WT+miR-NC、SOX2-OT-WT+miR-452-5p mimic、SOX2-OT-MUT+miR-NC、SOX2-OT-MUT+miR-452-5p mimic的萤光素酶活性分别为0.95 ± 0.11、0.42 ± 0.05、0.96 ± 0.11、0.99 ± 0.11。与miR-NC细胞比较,与SOX2-OT-WT共转染的miR-452-5p mimic萤光素酶活性降低($P < 0.05$)。

2.3　转染后各组细胞中lncRNA SOX2-OT、miR-452-

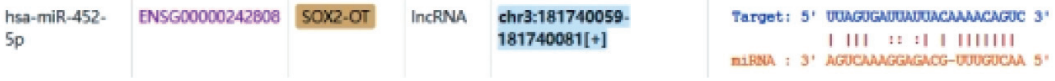



图1　starBase网站预测lncRNA SOX2-OT与miR-452-5p的靶向关系

Fig.1　Targeting relationship between lncRNA SOX2-OT and miR-452-5p predicted using the starBase website

5p水平

对照组、si-NC组、si-SOX2-OT组、si-SOX2-OT+anti-NC组、si-SOX2-OT+anti-miR-452-5p组lncRNA SOX2-OT水平分别为0.92 ± 0.10、0.91 ± 0.10、0.46 ± 0.06、0.48 ± 0.06、0.49 ± 0.06，miR-452-5p水平分别为0.39 ± 0.05、0.40 ± 0.05、0.87 ± 0.10、0.85 ± 0.10、0.43 ± 0.05。与si-NC组比较，si-SOX2-OT组lncRNA SOX2-OT水平降低，miR-452-5p水平升高（$P < 0.05$）；与si-SOX2-OT+anti-NC组比较，si-SOX2-OT+anti-miR-452-5p组miR-452-5p水平降低（$P < 0.05$）。

### 2.4　转染后各组细胞增殖情况

与si-NC组比较，si-SOX2-OT组EdU阳性率、PCNA、cyclin D1表达水平降低（$P < 0.05$）；与si-SOX2-OT+anti-NC组比较，si-SOX2-OT+anti-miR-452-5p组EdU阳性率、PCNA和cyclin D1表达水平升高（$P < 0.05$）。见图2、图3、表2。

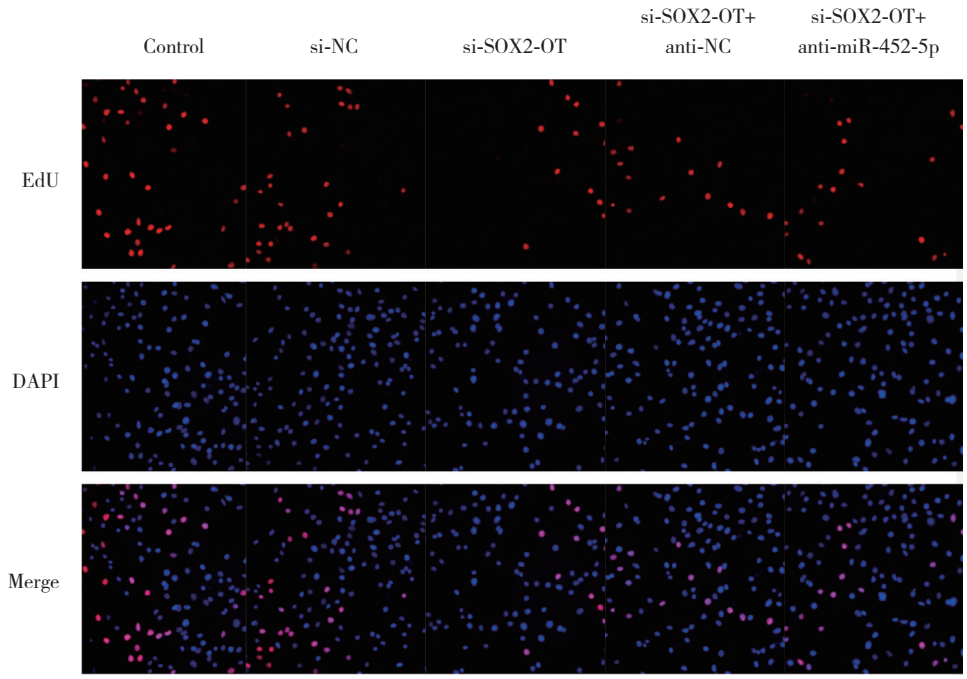
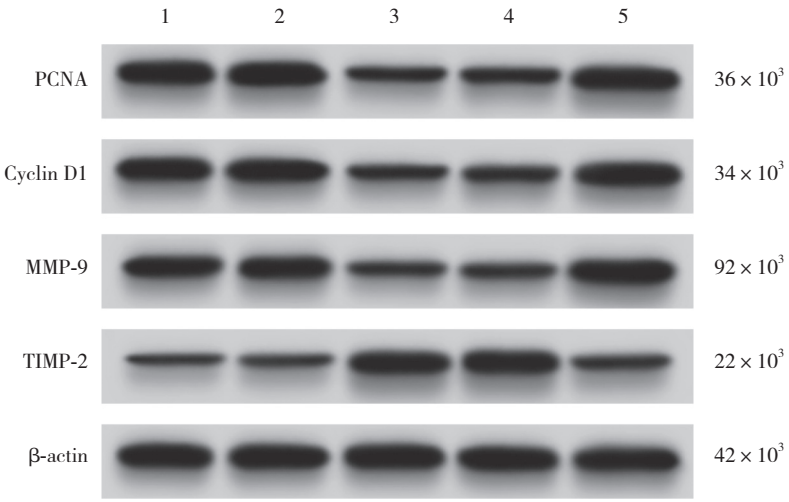



图2　EdU实验检测细胞增殖　×200

Fig.2　Cell proliferation detected using the EdU assay ×200




1，control group；2，si-NC group；3，si-SOX2-OT group；4，si-SOX2-OT+anti-NC group；5，si-SOX2-OT+anti-miR-452-5p group.

图3　Western blotting检测PCNA、cyclin D1、MMP-9、TIMP-2表达

Fig.3　PCNA，cyclin D1，MMP-9，and TIMP-2 expressions detected using Western blotting

2.5　转染后各组细胞迁移和侵袭情况

与si-NC组比较，si-SOX2-OT组迁移细胞数、侵袭细胞数、MMP-9表达水平降低，TIMP-2表达水平升高（$P < 0.05$）；与si-SOX2-OT+anti-NC组比较，si-SOX2-OT+anti-miR-452-5p组迁移细胞数、侵袭细胞数、MMP-9表达水平升高，TIMP-2表达水平降低（$P < 0.05$）。见图3、图4、表2。

2.6　裸鼠移植瘤

表2　各组细胞增殖、迁移和侵袭情况的比较

Tab.2　Comparison of cell proliferation，migration，and invasion among groups

| Group | $n$ | EdU (%) | PCNA | Cyclin D1 | Number of migrating cells | Number of invading cells | MMP-9 | TIMP-2 |
|---|---|---|---|---|---|---|---|---|
| Control | 6 | 35.68 ± 3.71 | 0.93 ± 0.10 | 0.85 ± 0.09 | 145.31 ± 15.86 | 122.45 ± 13.29 | 0.87 ± 0.10 | 0.34 ± 0.04 |
| si-NC | 6 | 34.71 ± 3.62 | 0.90 ± 0.10 | 0.84 ± 0.09 | 141.58 ± 15.22 | 121.36 ± 13.06 | 0.85 ± 0.10 | 0.37 ± 0.05 |
| si-SOX2-OT | 6 | 12.64 ± 1.35[1)] | 0.42 ± 0.05[1)] | 0.39 ± 0.05[1)] | 81.63 ± 8.37[1)] | 70.42 ± 7.18[1)] | 0.38 ± 0.05[1)] | 0.80 ± 0.09[1)] |
| si-SOX2-OT+anti-NC | 6 | 13.38 ± 1.43 | 0.43 ± 0.05 | 0.40 ± 0.05 | 83.47 ± 8.49 | 72.61 ± 7.35 | 0.40 ± 0.05 | 0.78 ± 0.09 |
| si-SOX2-OT+anti-miR-452-5p | 6 | 30.52 ± 3.19[2)] | 0.88 ± 0.10[2)] | 0.80 ± 0.09[2)] | 130.39 ± 14.03[2)] | 115.28 ± 12.47[2)] | 0.81 ± 0.09[2)] | 0.39 ± 0.05[2)] |

1) $P < 0.05$ vs. si-NC group; 2) $P < 0.05$ vs. si-SOX2-OT+anti-NC group.

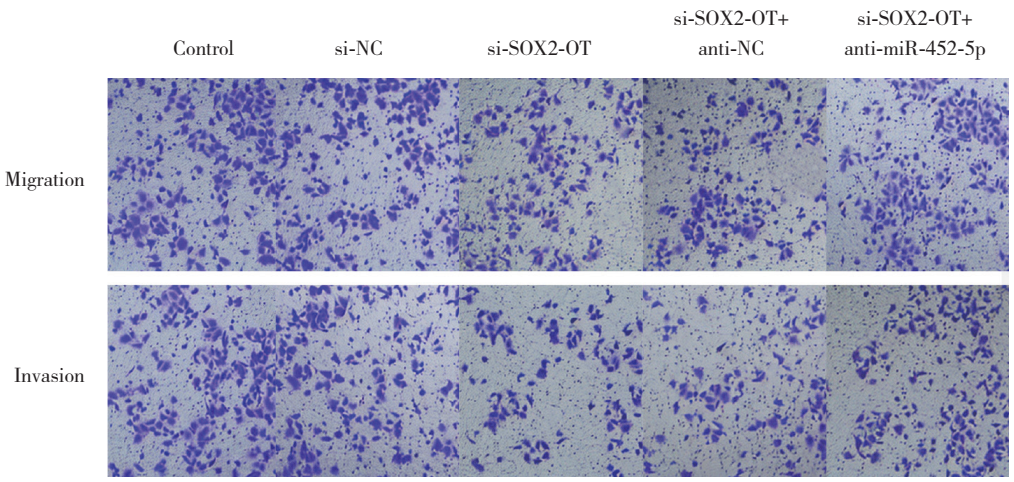


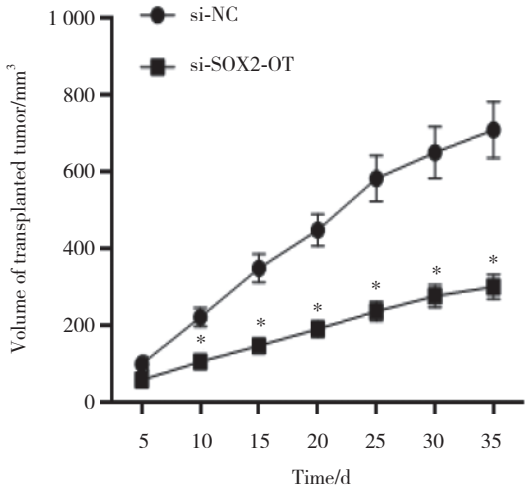

图4　Transwell实验检测细胞迁移和侵袭　×200

Fig.4　Cell migration and invasion detected using Transwell assay　×200

si-NC组和si-SOX2-OT组移植瘤体积分别为（711.49 ± 73.52）mm³和（302.57 ± 31.87）mm³，质量分别为（1.28 ± 0.14）g和（0.59 ± 0.07）g，lncRNA SOX2-OT水平分别为0.95 ± 0.11和0.51 ± 0.06，miR-452-5p水平分别为0.42 ± 0.05和0.91 ± 0.10。与si-NC组比较，si-SOX2-OT组移植瘤生长缓慢，体积减小，质量减轻，lncRNA SOX2-OT水平降低，miR-452-5p水平升高（$P < 0.05$）。见图5。

2.7　移植瘤组织病理形态

si-NC组肿瘤细胞异型性明显，细胞呈长椭圆形，细胞质染色不均，细胞核呈紫褐色类圆形，核分裂现象明显，核仁明显；si-SOX2-OT组瘤组织可见不同程度的出血和红染颗粒状坏死。见图6。




*$P < 0.05$ vs. si-NC group.

图5　裸鼠移植瘤体积

Fig.5　Volumes of transplanted tumors in nude mice

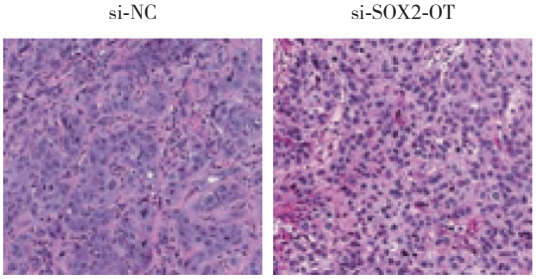



图6　HE染色观察裸鼠移植瘤病理变化　×200

Fig.6　Pathological changes in transplanted tumors in nude mice determined using HE staining　×200

## 3　讨论

宫颈癌是最常见的HPV相关疾病，主要是由HPV感染引起的宫颈前期病变，若不及时治疗，会发展为浸润癌[5]。随着经济和医疗技术的快速发展，在进行有效的宫颈癌筛查和HPV疫苗接种的国家，宫颈癌的发病率和死亡率呈稳定或下降趋势，而在医疗条件较差的国家，其发病率和死亡率居高不下[6]。尽早预防、诊断并采用新型治疗技术是当前提高宫颈癌患者生存率的重要策略。

宫颈癌的发生和发展与癌细胞的增殖、迁移和侵袭等多种恶性行为密切相关。本研究发现，在宫颈癌细胞中PCNA、cyclin D1、MMP-9高表达，TIMP-2低表达。PCNA、cyclin D1是癌细胞增殖相关蛋白，MMP-9和TIMP-2在癌细胞的迁移和侵袭进程中发挥重要作用。研究[7]表明，促进PCNA、cyclin D1表达可促进宫颈癌细胞的增殖，加快体内肿瘤的生长，进而促进宫颈癌发生和发展。抑制PCNA、cyclin D1表达可促进细胞周期停滞，抑制宫颈癌异种移植瘤的生长[8]。降低MMP9的表达可削弱SiHa细胞的侵袭和迁移能力，减慢肿瘤的生长，抑制宫颈癌的发生和发展[9]。TIMP2过表达可抑制宫颈鳞状细胞癌细胞生长和转移，促进癌细胞凋亡，抑制宫颈癌发展[10]。由此可推测，抑制PCNA、cyclin D1、MMP-9表达，促进TIMP-2表达，可抑制宫颈癌的增殖、迁移和侵袭，进而抑制宫颈癌的恶性进展。

lncRNA的异常表达参与多种疾病的发展进程，lncRNA SOX2-OT常作为致癌因子，参与调节癌细胞的多种恶性生物学行为，并作为预后和诊断生物标志物用于癌症治疗[11]。本研究发现，lncRNA SOX2-OT在宫颈癌组织和细胞中高表达，抑制lncRNA SOX2-OT可抑制宫颈癌细胞的增殖、迁移和侵袭。研究[12]显示，lncRNA SOX2-OT过表达可增强卵巢癌恶性表型，抑制lncRNA SOX2-OT可抑制卵巢癌的肿瘤生长。lncRNA SOX2-OT还可通过靶向抑制miR-519e-5p促进乳腺癌细胞增殖，降低乳腺细胞对放射的敏感性[13]。提示抑制lncRNA SOX2-OT可抑制宫颈癌细胞的恶性进展。

miRNA是常见的短链非编码RNA，其异常表达与包括宫颈癌在内的多种疾病的发生和发展密切相关。miRNA常受lncRNA靶向调控，参与癌症的发生和发展。本研究发现，miR-452-5p在宫颈癌组织和细胞中低表达，沉默lncRNA SOX2-OT可上调miR-452-5p，且二者间存在靶向结合位点，表明lncRNA SOX2-OT可靶向抑制miR-452-5p，促进宫颈癌发生和发展。研究[14]显示，miR-452-5p过表达可抑制宫颈癌细胞的增殖、迁移和侵袭，促进凋亡，进而抑制体内异种移植瘤的生长。过表达miR-452-5p可抑制非小细胞肺癌细胞的迁移、侵袭和增殖能力[15]。本研究中裸鼠实验结果显示，敲低lncRNA SOX2-OT可上调miR-452-5p水平，抑制裸鼠移植瘤的生长，表明沉默lncRNA SOX2-OT可通过靶向上调miR-452-5p，抑制宫颈癌发生和发展。

综上所述，lncRNA SOX2-OT可促进宫颈癌细胞增殖、迁移和侵袭，与靶向抑制miR-452-5p相关。但宫颈癌的发病机制受多方面调控，且其分子靶向基因具有多样性，后续研究还需从多方面进行深入探究。

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