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· 论著 ·

## HOXB7反义寡核苷酸对口腔鳞癌细胞迁移和运动能力的影响

邓晶, 邢育珍

(华中科技大学同济医学院附属协和医院口腔医学中心, 武汉 430022)

**[摘要]** 目的: 探讨HOXB7反义寡核苷酸对口腔鳞癌细胞迁移和运动能力的影响。方法: 在口腔鳞癌细胞系Tscca中转染HOXB7反义寡核苷酸和无义寡核苷酸, 记为AS-ODN和NS-ODN, 设置不转染寡核苷酸的细胞为Control, 采用real-time PCR和蛋白质印迹法检测细胞中HOXB7表达变化, MTT测定细胞增殖和黏附能力变化, 细胞划痕实验检测细胞运动能力, Transwell小室检测细胞侵袭和迁移能力, 蛋白质印迹法测定细胞中E-cadherin, N-cadherin, MMP-2, MMP-9表达水平。结果: HOXB7反义寡核苷酸转染后细胞中HOXB7表达水平降低, 细胞增殖、黏附、运动、侵袭和迁移能力均下降, 细胞中N-cadherin, MMP-2, MMP-9蛋白水平降低, E-cadherin蛋白水平升高, 与转染无义寡核苷酸的细胞比较, 差异具有统计学意义( $P < 0.05$ )。结论: HOXB7反义寡核苷酸具有抗口腔鳞癌细胞增殖、黏附、运动、侵袭、迁移和上皮-间充质转化的作用。

**[关键词]** 口腔鳞癌; HOXB7; 迁移; 运动; 黏附

## Effects of HOXB7 antisense oligonucleotides on migration and movement of oral squamous cell carcinoma

DENG Jing, XING Yuzhen

(Center of Stomatology, Union Medical College Affiliated to Tongji Medical College,  
Huazhong University of Science and Technology, Wuhan 430022, China)

**Abstract** **Objective:** To investigate the effects of HOXB7 antisense oligonucleotides on migration and movement of oral squamous cell carcinoma. **Methods:** HOXB7 antisense oligonucleotides and nonsense oligonucleotides were transfected into oral squamous cell carcinoma cell line Tscca, named as AS-ODN and NS-ODN. The cells that did not transfect oligonucleotides was named as Control. Real-time PCR and Western blot were used to detect the expression of HOXB7 in cells. Cell proliferation and adhesion ability were detected by MTT. Cell scratch test was used to detect cell motility. Transwell was used to detect cell invasion and migration. Western blot was used to detect the expression levels of E-cadherin, N-cadherin, MMP-2 and MMP-9 in cells. **Results:** After transfection of HOXB7 antisense oligonucleotides, the expression level of HOXB7 and cell proliferation, adhesion,

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通信作者 (Corresponding author): 邢育珍, Email: explore2009@163.com

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movement, invasion, migration decreased, the levels of N-cadherin, MMP-2 and MMP-9 in cells decreased, the level of E-cadherin protein increased, compared with the cells transfected with nonsense oligonucleotides, the difference were statistically significant( $P < 0.05$ ). **Conclusion:** HOXB7 antisense oligonucleotides can inhibit the proliferation, adhesion, movement, invasion, migration and EMT of oral squamous cell carcinoma cells.

**Keywords** oral squamous cell carcinoma; HOXB7; migration; movement; adhesion

口腔鳞癌是最为常见的发生于头颈部的恶性肿瘤, 目前人们对于其分子发病机制的研究一直没有中断, 基因靶向治疗也成为目前肿瘤治疗的热点。肿瘤致死的重要原因是肿瘤转移, 肿瘤细胞分子转移机制受到基因等的调控, 探索肿瘤细胞迁移、侵袭等机制是阐明肿瘤转移分子机制的基础<sup>[1-2]</sup>。同源盒基因B7(homeobox B7, HOXB7)是一种同源盒基因, 其在进化上具有高度保守性, 参与细胞分化、胚胎发育等过程, 其异常表达还与肿瘤的发生有关, 在口腔癌、胃癌等肿瘤中已经证实其高表达, 并且HOXB7的表达水平与肿瘤的转移、预后等有关, 下调其表达还可以减弱乳腺癌、结直肠癌等肿瘤细胞的侵袭能力<sup>[3-7]</sup>。目前对于HOXB7在口腔鳞癌细胞中的作用尚不明确。本研究探讨HOXB7反义寡核苷酸对口腔鳞癌细胞系TSCCA体外增殖、黏附、运动、侵袭、迁移能力的影响, 为阐明口腔鳞癌分子发病机制和靶向HOXB7治疗口腔鳞癌提供参考。

## 1 材料与方法

### 1.1 材料

口腔鳞癌细胞系TSCCA购自通派(上海)生物科技有限公司; SYBR Green Real-time PCR Maser Mix购自东洋纺(上海)生物科技有限公司; E-cadherin抗体购自美国Cell Signaling Technology公司; cDNA第一链反转录试剂盒购自江苏碧云天生物技术有限公司; MMP-9抗体购自上海酶联生物研究所; 脂质体Lipofectin购自美国Thermo公司; HOXB7抗体购自美国R&D Systems公司; MMP-2抗体、N-cadherin抗体购自美国Santa Cruze公司。

### 1.2 细胞转染及分组处理

TSCCA细胞分成Control, NS-ODN, AS-ODN组。Control组为不进行细胞转染的正常细胞, NS-ODN组和AS-ODN组分别为转染无义寡核苷酸(NS-ODN)和反义寡核苷酸(AS-ODN)序列的细胞, 核苷酸均由上海生工合成。选用10  $\mu\text{L}/\text{mL}$ 的Lipofectin条件下, NS-ODN, AS-ODN终浓度

为0.4  $\mu\text{mol}/\text{L}$ 进行转染(此时转染效率最高), 采用阳离子脂质体Lipofectin转染, 步骤同转染试剂说明书。

### 1.3 Real-time PCR检测细胞中HOXB7 mRNA表达水平

取转染后48 h的Control, NS-ODN, AS-ODN细胞, 以TRIzol试剂获取总RNA, 用cDNA第一链反转录试剂盒将RNA反转录合成cDNA, 以SYBR Green Real-time PCR Maser Mix进行real-time PCR并计算目的基因HOXB7的表达变化, 设置内参为GAPDH, 引物: HOXB7正向5'-TATGGGCTCGAGCCGAGTT-3', 反向5'-GGCCTCGTTTGC GGTCAGT-3'; GAPDH正向5'-TGCACCACCAACTGCTTAGC-3', 反向5'-GGCATGGACTGTGGTCATGAG-3'。PCR条件为95  $^{\circ}\text{C}$ 反应30 s, 然后在95  $^{\circ}\text{C}$ 反应5 s, 60  $^{\circ}\text{C}$ 反应30 s, 共40个循环。根据PCR反应的Ct值计算HOXB7表达水平。

### 1.4 蛋白质印迹法检测细胞中HOXB7蛋白质表达水平

取转染后48 h的Control, NS-ODN, AS-ODN细胞, 添加PMSF/RIPA溶液提取细胞中的总蛋白, 用BCA蛋白定量试剂盒检测蛋白浓度。分离胶浓度设定为10%, 浓缩胶浓度设定为5%。把蛋白与5 $\times$ Loading Buffer混合后煮沸5 min。每个孔中上样量为30  $\mu\text{g}$ , 设置80 V恒压电泳2 h, 观察到蛋白进入到底部时即停止电泳。把PVDF膜裁剪成合适大小, 以60 V电压转膜1.5 h后, 用5%脱脂奶粉封闭。一抗孵育条件为4  $^{\circ}\text{C}$ 过夜, 二抗孵育条件为室温2 h。把PVDF膜放在抗体孵育液中反应后, 采用ECL发光, 用凝胶图片处理软件分析光密度值, 内参为GAPDH。HOXB7一抗稀释倍数为1:1 000。

### 1.5 MTT检测细胞增殖

Control, NS-ODN, AS-ODN细胞按照单孔细胞数目为2 000个种植到96孔细胞培养板中。培养48 h以后, 进行MTT检测: 在每个孔中添加0.2 mg/mL的MTT溶液, 孵育4 h以后, 以1 000 r/min离心10 min, 把上清吸除以后, 添加DMSO溶液

150  $\mu\text{L}$ 。利用酶标仪检测490 nm的光密度值。设置Control细胞存活率为100%，分析NS-ODN, AS-ODN细胞存活率变化。

### 1.6 MTT评估细胞黏附

用10  $\mu\text{g}/\text{mL}$ 的FN将96孔细胞培养板包被后在4  $^{\circ}\text{C}$ 过夜, 添加0.1%的牛血清白蛋白洗涤以后, 添加0.5%牛血清白蛋白置于37  $^{\circ}\text{C}$ 孵育1 h。把Control, NS-ODN, AS-ODN组细胞分别种植到96孔板中, 每孔 $4 \times 10^4$ 个细胞, 常规方法孵育50 min以后, 把没有黏附的细胞用PBS洗掉, 加入MTT溶液孵育4 h以后弃掉, 添加DMSO溶液, 测定490 nm的吸光度值。设置Control黏附率为100%, 分析NS-ODN, AS-ODN细胞黏附率变化。

### 1.7 细胞划痕实验评估细胞运动能力

Control, NS-ODN, AS-ODN组细胞种植到6孔板中, 细胞生长密度为90%时, 把孔内的液体吸弃, 用移液枪在6孔板的中央划出1条细痕, 以PBS洗涤后, 添加不含血清的细胞培养液, 分别测定0和48 h时划痕的宽度。计算细胞间隙融合率, 间隙融合率=100% $\times$ (0 h划痕宽度-48 h划痕宽度) $\div$ 0 h划痕宽度。

### 1.8 Transwell小室评估细胞侵袭和迁移能力

取出Matrigel置于4  $^{\circ}\text{C}$ 中解冻, 用不含血清的DMEM稀释以后, 添加至Transwell小室中, 37  $^{\circ}\text{C}$ 孵育2 h。Control, NS-ODN, AS-ODN组细胞用不含血清的细胞培养液悬浮以后, 把细胞密度调整到 $1 \times 10^5$ 个/mL。将Transwell小室置于24孔板中, 在下室中添加600  $\mu\text{L}$ 的培养液, 在上室中分别

添加200  $\mu\text{L}$ 的上述Control, NS-ODN, AS-ODN组细胞悬浮液, 培养48 h以后, 在多聚甲醛中固定, 结晶紫染色处理以后, 用蒸馏水冲洗。在显微镜下观察细胞穿膜数量即为侵袭数目。细胞迁移实验之前不需要用Matrigel处理小室, 其余步骤相同。

### 1.9 蛋白质印迹法检测细胞中E-cadherin, N-cadherin, MMP-2, MMP-9蛋白表达水平

Control, NS-ODN, AS-ODN组细胞培养48 h以后, 用蛋白质印迹法测定细胞中E-cadherin, MMP-2, N-cadherin, MMP-9蛋白水平, E-cadherin抗体、N-cadherin抗体以1:800稀释, MMP-2抗体、MMP-9抗体以1:600稀释。

### 1.10 统计学处理

用SPSS 21.0软件进行数据分析, 计量资料用均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示, 多组差异比较采用单因素方差分析, 组间比较用LSD-*t*检验,  $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 HOXB7反义寡核苷酸对口腔鳞癌细胞中HOXB7表达的影响

口腔鳞癌细胞中转染HOXB7反义寡核苷酸后, 细胞中的HOXB7 mRNA和蛋白水平均降低(图1)。

### 2.2 下调HOXB7对口腔鳞癌细胞增殖和黏附影响

下调HOXB7后的口腔鳞癌细胞存活率和黏附率均下降, 下调HOXB7抑制口腔鳞癌细胞增殖和黏附(图2)。

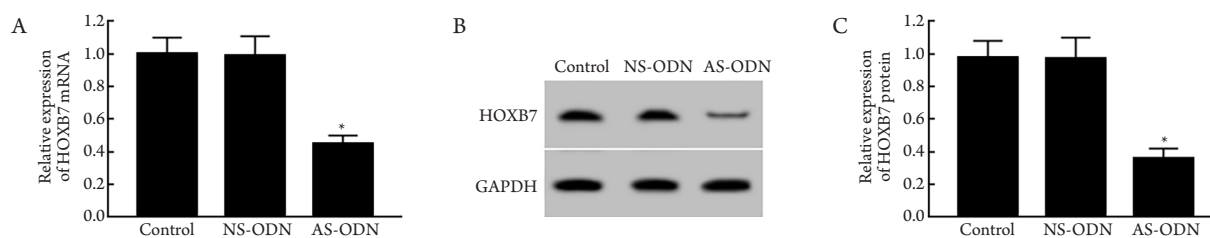


图1 HOXB7反义寡核苷酸转染后细胞中HOXB7表达变化

Figure 1 Changes of HOXB7 expression in cells transfected with HOXB7 antisense oligonucleotides

(A) Real-time PCR检测HOXB7 mRNA相对表达水平( $F=33.13$ ,  $P < 0.01$ ); (B) 蛋白质印迹法检测HOXB7蛋白表达水平; (C)以GAPDH作为参照, HOXB7蛋白相对表达水平( $F=37.21$ ,  $P < 0.01$ )。与NS-ODN比较,  $*P < 0.05$ 。

(A) Real-time PCR was used to detect the relative expression level of HOXB7 mRNA ( $F=33.13$ ,  $P < 0.01$ ); (B) Western blot was used to detect the expression of HOXB7 protein; (C) With GAPDH as the reference, the relative expression level of HOXB7 protein ( $F=37.21$ ,  $P < 0.01$ ). Compared with NS-ODN,  $*P < 0.05$ .

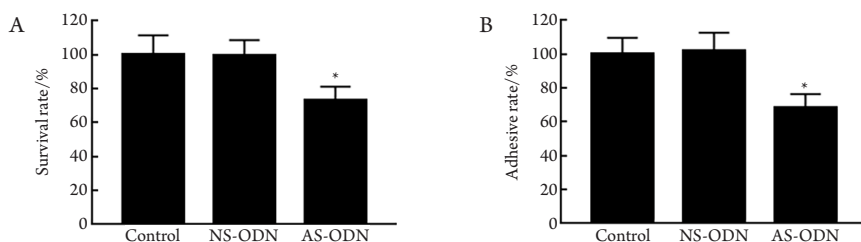


图2 下调HOXB7后口腔鳞癌细胞增殖和黏附能力变化

**Figure 2 Changes of proliferation and adhesion of oral squamous cell carcinoma cells after down-regulation of HOXB7**

(A) 下调HOXB7后口腔鳞癌细胞存活率比较( $F=7.77$ ,  $P=0.02$ ); (B) 下调HOXB7后口腔鳞癌细胞黏附率比较( $F=11.68$ ,  $P=0.01$ )。与NS-ODN比较,  $*P<0.05$ 。

(A) Survival rate of oral squamous cell carcinoma cells after HOXB7 down-regulation ( $F=7.77$ ,  $P=0.02$ ); (B) Adhesion rate of oral squamous cell carcinoma cells after HOXB7 down-regulation ( $F=11.68$ ,  $P=0.01$ ). Compared with NS-ODN,  $*P<0.05$ .

**2.3 下调HOXB7对口腔鳞癌细胞运动能力的影响**

下调HOXB7后的口腔鳞癌细胞间隙融合率下降, 下调HOXB7抑制口腔鳞癌细胞运动能力(图3)。

**2.4 下调HOXB7对口腔鳞癌细胞迁移和侵袭能力的影响**

下调HOXB7后的口腔鳞癌细胞迁移数目及侵

袭数目均下降, 下调HOXB7抑制口腔鳞癌细胞迁移和侵袭能力(图4)。

**2.5 下调HOXB7对口腔鳞癌细胞中E-cadherin, N-cadherin, MMP-2, MMP-9蛋白表达的影响**

下调HOXB7后的口腔鳞癌细胞中N-cadherin, MMP-2, MMP-9蛋白水平均下降, E-cadherin蛋白水平升高(图5)。

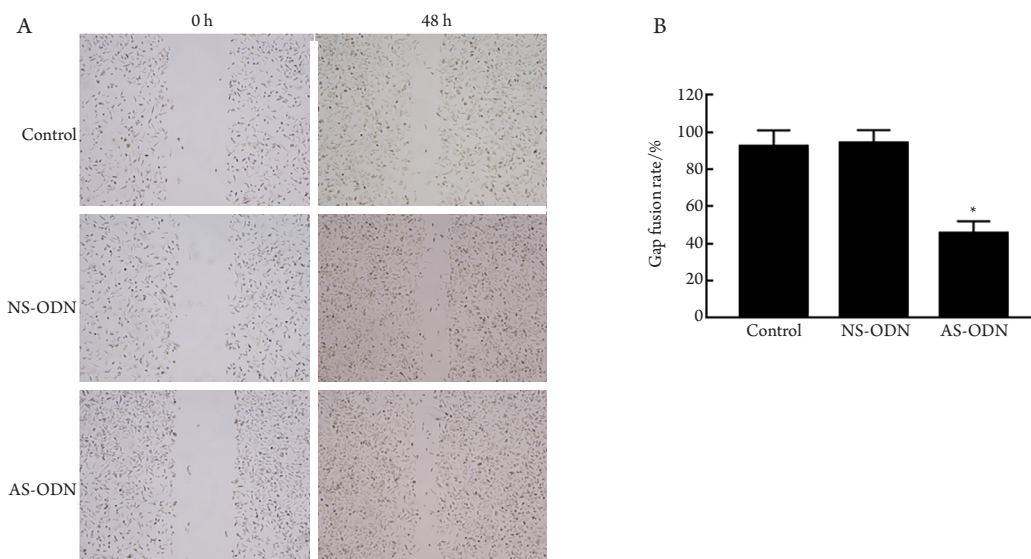


图3 下调HOXB7后口腔鳞癌细胞运动能力变化

**Figure 3 Changes of cell motility in oral squamous cell carcinoma after down-regulation of HOXB7**

(A) 细胞划痕实验结果; (B) 细胞间隙融合率比较( $F=40.30$ ,  $P<0.01$ )。与NS-ODN比较,  $*P<0.05$ 。

(A) Cell scratch test results; (B) Comparison of gap fusion rate ( $F=40.30$ ,  $P<0.01$ ). Compared with NS-ODN,  $*P<0.05$ .

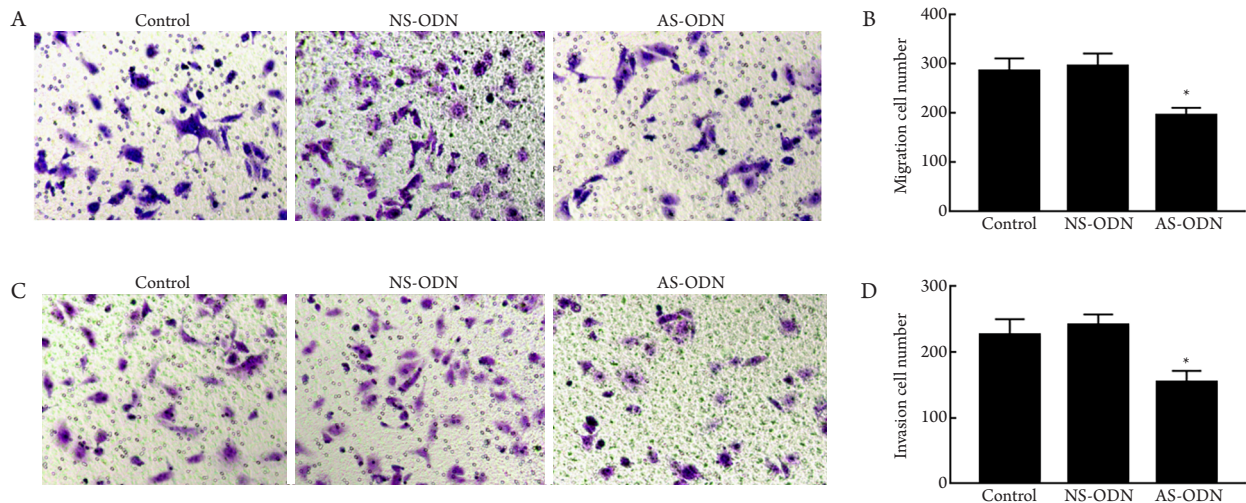


图4 下调HOXB7后口腔鳞癌细胞侵袭和迁移能力变化

Figure 4 Changes of invasion and migration of oral squamous cell carcinoma cells after down-regulation of HOXB7

(A) Transwell小室检测下调HOXB7后口腔鳞癌细胞迁移情况( $\times 200$ ); (B) 口腔鳞癌细胞迁移数目( $F=17.44$ ,  $P<0.01$ ); (C) Transwell小室检测下调HOXB7后口腔鳞癌细胞侵袭情况( $\times 200$ ); (D) 口腔鳞癌细胞侵袭数目( $F=18.03$ ,  $P<0.01$ )。与NS-ODN比较,  $*P<0.05$ 。

(A) Transwell chamber was used to detect the migration of oral squamous cell carcinoma cells after down-regulation of HOXB7 ( $\times 200$ ); (B) The number of cell migration in oral squamous cell carcinoma ( $F=17.44$ ,  $P<0.01$ ); (C) Transwell chamber was used to detect the invasion of oral squamous cell carcinoma cells after down-regulation of HOXB7 ( $\times 200$ ); (D) Invasion number of oral squamous cell carcinoma cells ( $F=18.03$ ,  $P<0.01$ ). Compared with NS-ODN,  $*P<0.05$ .

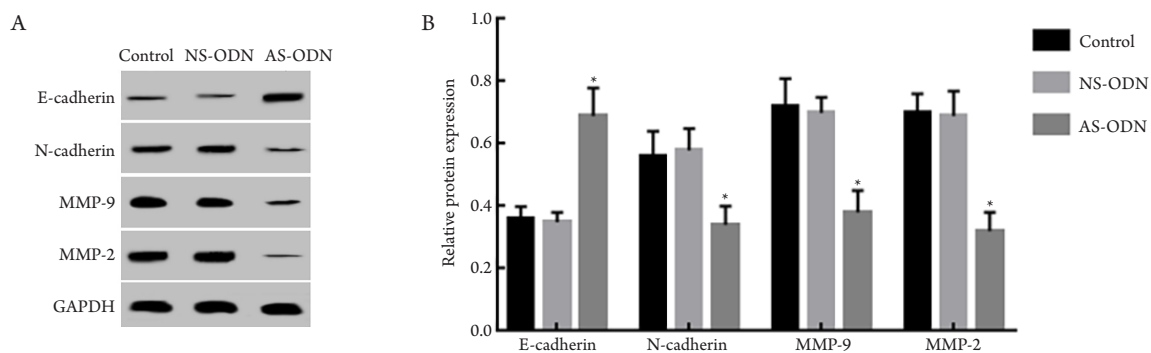


图5 下调HOXB7后口腔鳞癌细胞中E-cadherin, N-cadherin, MMP-2, MMP-9蛋白表达变化

Figure 5 Downregulation of E-cadherin, N-cadherin, MMP-2 and MMP-9 protein expression in oral squamous cell carcinoma cells after HOXB7 treatment

(A) 蛋白质印迹法检测下调HOXB7后口腔鳞癌细胞中E-cadherin, N-cadherin, MMP-2, MMP-9蛋白表达水平; (B) 以GAPDH作为参照, 口腔鳞癌细胞中E-cadherin, N-cadherin, MMP-2, MMP-9蛋白水平。与NS-ODN比较,  $*P<0.05$ ;  $F_{E-cadherin}=31.78$ ,  $P_{E-cadherin}<0.001$ ;  $F_{N-cadherin}=10.71$ ,  $P_{N-cadherin}=0.01$ ;  $F_{MMP-2}=31.04$ ,  $P_{MMP-2}<0.001$ ;  $F_{MMP-9}=21.14$ ,  $P_{MMP-9}<0.01$ 。

(A) Western blot was used to detect the expression of E-cadherin, N-cadherin, MMP-2 and MMP-9 in oral squamous cell carcinoma cells after HOXB7 was down-regulated; (B) With GAPDH as a reference, the levels of E-cadherin, N-cadherin, MMP-2 and MMP-9 proteins in oral squamous cell carcinoma cells were measured. Compared with NS-ODN,  $*P<0.05$ ;  $F_{E-cadherin}=31.78$ ,  $P_{E-cadherin}<0.001$ ;  $F_{N-cadherin}=10.71$ ,  $P_{N-cadherin}=0.01$ ;  $F_{MMP-2}=31.04$ ,  $P_{MMP-2}<0.001$ ;  $F_{MMP-9}=21.14$ ,  $P_{MMP-9}<0.01$ .

### 3 讨论

HOXB7在胚胎早期的中枢神经系统、后肠等组织中广泛表达,而在胚胎发育的后期只在特定的组织中表达,HOXB7在成人的子宫内膜、小脑、扁桃体等少数组织中表达。HOXB7是在肿瘤新生血管形成中发现的,推测其与肿瘤的转移有关<sup>[8-10]</sup>。目前对于HOXB7在肿瘤中的研究<sup>[11-12]</sup>表明:HOXB7参与结直肠癌、卵巢癌等肿瘤细胞运动和侵袭过程,HOXB7在肿瘤组织中高表达与肿瘤患者的预后等有关。对口腔鳞癌的研究<sup>[13-14]</sup>报道:HOXB7在口腔鳞癌组织和细胞中过表达,并且过表达HOXB7可以逆转miR-376c-3p的抗口腔鳞癌细胞生长和迁移的作用,过表达HOXB7可能发挥促进口腔鳞癌的作用。

本实验选用口腔鳞癌细胞系Tscca,通过细胞转染反义寡核苷酸下调细胞中HOXB7表达水平,发现下调HOXB7可以降低口腔鳞癌细胞的增殖、运动、侵袭、迁移能力以及MMP-2, MMP-9蛋白表达水平,证实HOXB7可能具有正调控口腔鳞癌转移的作用,这与之前的研究<sup>[13-14]</sup>报道一致,均说明HOXB7可能具有促进口腔鳞癌转移的作用。肿瘤转移是肿瘤患者死亡的重要原因之一,肿瘤细胞转移是一个复杂过程,肿瘤细胞从原发位置脱落以后进入到细胞外基质中,通过分泌细胞外基质降解酶MMP-2, MMP-9等降解细胞外基质,从而侵入淋巴管或血管,通过与内皮细胞等在靶点处黏附而穿出脉管,肿瘤细胞通过恶性增殖形成新的转移灶<sup>[15]</sup>。在胰腺癌、胃癌等肿瘤细胞中已经证实,HOXB7表达下降可以抑制肿瘤细胞侵袭和迁移能力,下调HOXB7可能是抑制肿瘤转移的方法之一<sup>[16-17]</sup>。本实验证实了HOXB7在口腔鳞癌细胞增殖、黏附、运动、迁移、侵袭中的作用,下调HOXB7在口腔鳞癌细胞中的作用与其他肿瘤相同,均可以抵抗肿瘤细胞恶性转移表型。

研究<sup>[18]</sup>显示:肿瘤细胞EMT发生于肿瘤转移前,肿瘤细胞EMT也被认为是肿瘤转移的标志之一。正常情况下,EMT发生于组织分化、胚胎发育等过程中,病理条件下,EMT与肿瘤、肺组织纤维化等有关<sup>[19]</sup>。EMT是细胞上皮细胞特征逐渐消失而逐渐出现间质细胞表型的过程,在这一过程中上皮标志物E-cadherin水平降低,而间质标志物N-cadherin水平逐渐升高<sup>[20-21]</sup>。本实验表明:下调HOXB7以后的口腔鳞癌细胞中E-cadherin水平升高,而N-cadherin水平降低,说明下调HOXB7能够抑制口腔鳞癌细胞EMT,进一步证实了HOXB7在

口腔鳞癌转移中的作用。

综上,下调HOXB7对于口腔鳞癌细胞增殖、运动、黏附、侵袭、迁移和EMT具有抑制作用,下调HOXB7可能具有抗口腔鳞癌转移的作用,后续还需要在体内和多株口腔鳞癌细胞中进行验证,这对于基因靶向治疗口腔鳞癌具有重要意义,为研究口腔鳞癌分子发生和转移机制提供了参考资料。

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