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在线全文

*circFOXP1*靶向miR-4429调控鼻咽癌6-10B细胞的增殖、迁移及侵袭*

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【摘要】 **目的** 探讨环状RNA叉头框蛋白P1（circular RNA forkhead box protein P1, *circFOXP1*）是否通过靶向miR-4429调控鼻咽癌6-10B细胞的增殖、迁移及侵袭。**方法** 分析*circFOXP1*和miR-4429表达与鼻咽癌患者病理特征的关系。在鼻咽癌6-10B细胞中分别转染si-NC、si-circFOXP1、pcDNA、pcDNA-circFOXP1、miR-NC、miR-4429模拟物，或同时转染si-circFOXP1与anti-miR-NC、anti-miR-4429。应用实时定量聚合酶链反应（qRT-PCR）检测鼻咽癌组织中*circFOXP1*和miR-4429的表达水平；采用细胞计数试剂盒8（CCK-8）、克隆形成实验、划痕实验及Transwell实验分别评估细胞活力、克隆形成能力、迁移能力及侵袭能力；Western blot法检测上皮型钙黏蛋白（E-cadherin）和神经型钙黏蛋白（N-cadherin）的表达；双萤光素酶报告基因实验验证*circFOXP1*与miR-4429的靶向关系。**结果** 鼻咽癌组织中*circFOXP1*的表达水平（4.61±0.31）较癌旁组织（1.00±0.05）升高（P<0.001），miR-4429的表达水平（0.37±0.03）较癌旁组织（1.00±0.08）降低（P<0.001）。*circFOXP1*表达与TNM分期相关（P<0.05），与肿瘤体积无显著相关性（P>0.05）；miR-4429表达与肿瘤体积和TNM分期均相关（P<0.05）。抑制*circFOXP1*表达或过表达miR-4429均可降低鼻咽癌6-10B细胞的活力、克隆形成数、划痕愈合率、侵袭细胞数及N-cadherin蛋白表达，同时升高E-cadherin蛋白表达（P<0.05）。*circFOXP1*可靶向并负向调控miR-4429的表达。干扰miR-4429能够逆转*circFOXP1*沉默对鼻咽癌细胞增殖、迁移及侵袭的抑制作用（P<0.05）。**结论** 抑制*circFOXP1*表达可通过靶向miR-4429减弱鼻咽癌6-10B细胞的增殖、迁移及侵袭能力。

【关键词】 鼻咽癌6-10B细胞 *circFOXP1* miR-4429 增殖 迁移 侵袭

circFOXP1 Targets miR-4429 to Regulate Proliferation, Migration and Invasion of Nasopharyngeal Carcinoma 6-10B Cells

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[**Abstract**] **Objective** To determine whether circular RNA forkhead box protein P1 (*circFOXP1*) regulates the proliferation, migration and invasion of nasopharyngeal carcinoma 6-10B cells by targeting miR-4429. **Methods** The correlations of *circFOXP1* and miR-4429 with pathological characteristics of nasopharyngeal carcinoma patients were analyzed. Nasopharyngeal carcinoma 6-10B cells were transfected with si-NC, si-circFOXP1, pcDNA, pcDNA-circFOXP1, miR-NC, miR-4429 mimics, or co-transfected with si-circFOXP1 and anti-miR-NC, or si-circFOXP1 and anti-miR-4429. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to detect *circFOXP1* and miR-4429 expression in nasopharyngeal carcinoma tissues. Cell viability, colony formation, migration and invasion abilities were assessed by Cell Counting Kit-8 (CCK-8), colony formation, wound healing and Transwell assays. Western blotting was used to detect E-cadherin and N-cadherin protein expression. A dual-luciferase reporter assay verified the targeting relationship between *circFOXP1* and miR-4429. **Results** The expression level of *circFOXP1* in nasopharyngeal carcinoma tissues (4.61 ± 0.31) was significantly higher than that in adjacent tissues (1.00 ± 0.05) (P < 0.001), while the expression level of miR-4429 (0.37 ± 0.03) was significantly lower than that in adjacent tissues (1.00 ± 0.08) (P < 0.001). The expression of miR-4429 was correlated with tumor volume and TNM stage (P < 0.05), while the expression of *circFOXP1* was correlated with TNM stage(P < 0.05) but not with tumor volume (P > 0.05). Inhibition of *circFOXP1* expression or overexpression of miR-4429 reduced cell viability, colony formation number, wound healing rate, invasive cell number and N-cadherin protein expression, while increased E-cadherin protein expression in nasopharyngeal carcinoma 6-10B cells (P < 0.05). *circFOXP1* targeted and negatively regulated miR-4429 expression. Interference with miR-4429 reversed the inhibitory effects of

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circFOXP1 silencing on proliferation, migration and invasion of nasopharyngeal carcinoma cells ($P < 0.05$). **Conclusion** Inhibition of *circFOXP1* expression can attenuate the proliferation, migration and invasion of nasopharyngeal carcinoma 6-10B cells by targeting miR-4429.

[Key words] Nasopharyngeal carcinoma 6-10B cells　*circFOXP1*　miR-4429　Proliferation　Migration　Invasion

鼻咽癌是一种发生于鼻咽黏膜中的恶性肿瘤，常见于中国南部和东南亚地区[1]。鼻咽癌大多数病理类型是非角质化的，具有高度恶性、侵袭性和转移性的特点[2]。由于早期鼻咽癌通常发生在难以察觉的隐蔽空间（例如咽部凹陷和上壁）中，多数患者在就医时病情已经恶化到晚期，预后极差[3]。因此，从基因异常的角度解释鼻咽癌的发生和发展对确定诊断和预后指标以及新药靶点具有重要意义。

与线性RNA不同，环状RNA（circular RNA, circRNA）具有共价闭合的环状结构，缺乏5′→3′极性及多聚腺苷酸尾巴。大量研究表明，circRNA在肿瘤的转移、凋亡、增殖等生物学过程中发挥着重要作用[4]。例如*circITCH*通过调节miR-224-3p轴增加鼻咽癌细胞的增殖和侵袭[5]，*circADARB1*通过增强*ZEB1*来促进鼻咽癌的生长和转移[6]。环状RNA叉头框蛋白P1（circRNA forkhead box P1, *circFOXP1*）是一种新发现的circRNA，被发现可以促进肝细胞癌[7]、胃癌[8]、肺癌[9]的进展，然而*circFOXP1*在鼻咽癌中的作用仍不清楚。

作为竞争性内源性RNA（competing endogenous RNAs, ceRNA），circRNA可以结合微小RNA（microRNA, miRNA）并抑制其功能[10]。近年来的研究发现，miR-4429可能在肿瘤进展中起重要作用。例如，ZHENG等[11]报告miR-4429通过靶向*PBX3*抑制胃癌的恶性发展。ZHOU等[12]确定miR-4429通过*Wnt*/β-Catenin途径抑制肺腺癌细胞的增殖和克隆形成。但是，miR-4429与鼻咽癌和*circFOXP1*的关系还需要进一步阐明。本研究主要目的考察*circFOXP1*在鼻咽癌组织中的表达，以及*circFOXP1*是否通过调控miR-4429参与鼻咽癌6-10B细胞的进展。

1　资料与方法

1.1　一般资料

选取2020年1月–2024年12月新乡市中心医院确诊的37例鼻咽癌及其癌旁组织作为研究对象，所有患者均为初诊，未接受放疗、化疗，鼻咽癌组织和癌旁组织样本保存在−80 ℃，直至RNA提取。本研究经新乡市中心医院伦理委员会批准，批件号：2020-1390-01（K），患者均知情同意。

鼻咽癌细胞株6-10B（美国ATCC）；*circFOXP1* siRNA（si-circFOXP1）、siRNA阴性对照si-NC、*circFOXP1*过表达载体pcDNA-circFOXP1（BamHI-NM_001244808-EcoRI通过这两个内切酶连接到pcDNA载体上）、过表达空载体pcDNA、miR-4429模拟物及抑制剂anti-miR-4429、其阴性对照miR-NC及anti-miR-NC（广州RiboBio）；于大连TaKaRa购置PrimeScript RT试剂、SYBR Green qPCR Mix试剂；上海Yeasen公司提供了细胞计数试剂盒8（Cell Counting Kit-8, CCK-8）；于美国Abcam公司购买了上皮型钙黏蛋白（E-cadherin）和神经型钙黏蛋白（N-cadherin）抗体；PVDF膜（美国Life Technologies）。

1.2　细胞分组

鼻咽癌6-10B细胞在添加了10%胎牛血清的DMEM培养基中，于体积分数为5%CO_2培养箱中生长，温度为37 ℃。将鼻咽癌6-10B细胞以1×10^5细胞/孔的浓度接种到6孔板中，培养至融合度达到70% ~ 80%，然后使用Lipofectamine 2000进行细胞转染。在鼻咽癌6-10B细胞中分别转染si-NC、si-circFOXP1（5′-TGACACGGGAACTTTAGAAATGATT-3′）、pcDNA、pcDNA-circFOXP1、miR-NC、miR-4429模拟物，或同时转染si-circFOXP1和anti-miR-NC、si-circFOXP1和anti-miR-4429。转染6 h后更换新鲜的完全培养基。48 h后通过qRT-PCR测定转染效率。

1.3　qRT-PCR测定

鼻咽癌组织或6-10B细胞总RNA由TRIzol试剂提取，并使用PrimeScript RT试剂逆转录为互补DNA（cDNA）。使用SYBR Green qPCR Mix对获得的cDNA进行qRT-PCR。*GAPDH*和*U6*作为内部参照，*circFOXP1*和miR-4429相对表达水平由$2^{-\Delta\Delta Ct}$法计算。引物序列如下：

*circFOXP1*正向：5'-CCACATGCCTCTACCAATGGA-3'，反向：5'-CAGCACTTGTTGCTGGAGGAT-3'；*GAPDH*正向：5'-CAGGAGGCATTGCTGATGAT-3'，反向：5'-GAAGGCTGGGGCTCATTT-3'；miR-4429正向：5'-GGCCAGGCAGTCTGAGTTG-3'，反向：5'-GGGAGAAAAGCTGGGCTGAG-3'；*U6*正向：5'-GCTTCGGCAGCACATATACTAAAAT-3'，反向：5'-CGCTTCACGAATTTGCGTGTCAT-3'。

1.4　细胞增殖测定

为了检测细胞活力，将鼻咽癌6-10B细胞以2×10^3/孔

的浓度接种于96孔板,在37 ℃下培养48 h后,每孔加入含10% CCK-8试剂的100 μL培养基,孵育2 h后测量450 nm波长处吸光度(OD)值。对于克隆形成实验,在6孔板中接种肿瘤细胞(3×10^2/孔),培养14 d后,将克隆用0.1%结晶紫染色15 min,然后在显微镜下计数克隆形成数。

1.5 细胞迁移测定

将鼻咽癌6-10B细胞(1×10^5/孔)接种于6孔板中培养24 h。随后,用无菌塑料移液管吸头垂直刮擦单层细胞,用磷酸盐缓冲液洗涤2次,在无血清DMEM中培养24 h。于0 h和24 h在倒置显微镜下观察划痕宽度,并用ImageJ软件分析,以划痕愈合率(%)反映细胞迁移能力。

1.6 细胞侵袭测定

通过Transwell法测定细胞侵袭能力:将20 μL Matrigel(原液9 mg/mL,用无血清DMEM按1∶9稀释)铺于8 μm孔径的Transwell上室,37 ℃孵育1 h。将鼻咽癌6-10B细胞以1×10^5/孔的浓度接种于上室,下室加入含20%胎牛血清的DMEM 500 μL,培养24 h。用甲醇固定侵袭至下室表面的细胞,结晶紫染色15 min,显微镜下计数5个视野的细胞数。

1.7 Western blot测定

使用RIPA裂解液从鼻咽癌6-10B细胞中提取总蛋白,经10% SDS-PAGE分离后转移至PVDF膜。封闭2 h后,将膜与一抗(抗E-cadherin、抗N-cadherin、抗GAPDH,均1∶1000稀释)4 ℃孵育过夜,然后与HRP标记的二抗(1∶5000)室温孵育1 h。ECL化学发光法检测蛋白信号,ImageJ软件分析灰度值。

1.8 双萤光素酶报告基因实验

利用StarBase数据库预测miR-4429与*circFOXP1*的结合位点。通过PCR扩增含有miR-4429结合位点的*circFOXP1*序列,克隆构建野生型(WT)-circFOXP1报告载体;采用定点诱变技术构建突变型(MUT)-circFOXP1报告载体。将报告载体与miR-4429模拟物或miR-NC共转染至6-10B细胞,48 h后使用Promega双萤光素酶报告基因检测系统测定萤光素酶活性。

1.9 统计学方法

采用SPSS 22.0软件进行数据分析。符合正态分布的计量数据以$\bar{x}\pm s$表示。两组间比较采用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Bonferroni校正。α=0.05。

2 结果

2.1 鼻咽癌组织中 *circFOXP1*和miR-4429的表达情况

如表1所示,与癌旁组织比较,鼻咽癌组织中*circFOXP1*表达水平升高(P<0.001),miR-4429表达水平降低(P<0.001)。根据*circFOXP1*和miR-4429的中位数表达水平,将37例患者分为高表达组和低表达组。如表2所示,miR-4429表达与肿瘤体积和TNM分期相关(P<0.05);*circFOXP1*表达与TNM分期相关(P<0.05),但与肿瘤体积无显著相关性(P>0.05)。

表 1 *circFOXP1*和miR-4429在37例鼻咽癌组织中的表达

Table 1 Expression of *circFOXP1* and miR-4429 in 37 nasopharyngeal carcinoma tissues

Tissue	*circFOXP1*	miR-4429
Adjacent tissues	1.00 ± 0.05	1.00 ± 0.08
Nasopharyngeal carcinoma	4.61 ± 0.31	0.37 ± 0.03
t	69.931	44.852
P	< 0.001	< 0.001

表 2 *circFOXP1*和miR-4429表达水平与鼻咽癌患者临床病理特征的关系

Table 2 Relationship between the expression levels of *circFOXP1* and miR-4429 and the clinical and pathological characteristics of patients with nasopharyngeal carcinoma

Characteristic	Case (n = 37)	*circFOXP1* expression level		P	miR-4429 expression level		P
		Low (n = 18)	High (n = 19)		Low (n = 18)	High (n = 19)	
Sex				0.6028			0.2363
Male	21	11	10		12	9	
Female	16	7	9		6	10	
Age				0.8728			0.6185
≤ 60 yr.	19	9	10		10	9	
> 60 yr.	18	9	9		8	10	
Tumor size				0.1376			0.0305
< 3 cm	23	9	14		8	16	
≥ 3 cm	14	9	5		11	3	
TNM stage				0.0086			0.0159
Ⅰ/Ⅱ	11	9	2		2	9	
Ⅲ/Ⅳ	26	9	17		16	10	

2.2　抑制 *circFOXP1*表达对鼻咽癌6-10B细胞增殖的影响

如图1和表3所示，与si-NC组比较，si-circFOXP1组*circFOXP1*表达水平降低（$P<0.05$），同时细胞活力和克隆形成数也降低（$P<0.05$）。

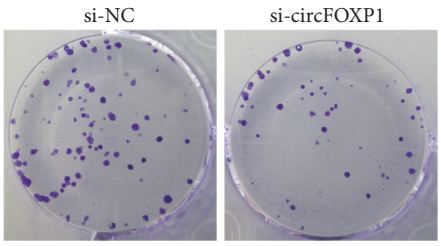

图 1　干扰 *circFOXP1*影响6-10B细胞增殖

Fig 1　Interference with *circFOXP1* affects the proliferation of 6-10B cells

表 3　抑制 *circFOXP1*表达对鼻咽癌6-10B细胞增殖的影响（*n*=9）

Table 3　The effect of inhibiting the expression of *circFOXP1* on the proliferation of nasopharyngeal carcinoma 6-10B cells (*n* = 9)

Group	*circFOXP1*	OD_{450}	Number of colonies
si-NC	1.00 ± 0.00	1.08 ± 0.08	79.14 ± 7.44
si-circFOXP1	0.23 ± 0.02	0.57 ± 0.05	32.57 ± 3.17
t	115.500	16.218	17.275
P	< 0.001	< 0.001	< 0.001

2.3　*circFOXP1*沉默抑制6-10B细胞迁移和侵袭

如图2和表4所示，与si-NC组比较，si-circFOXP1组划痕愈合率、侵袭细胞数和N-cadherin蛋白表达降低，而E-cadherin蛋白表达增加（$P<0.05$）。

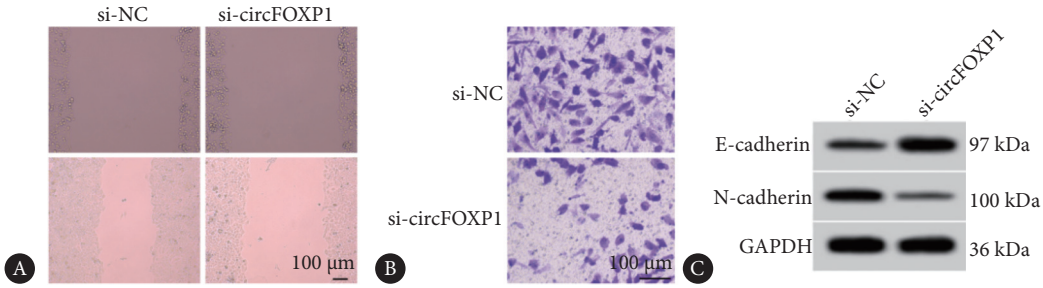

图 2　敲低 *circFOXP1*对6-10B细胞迁移侵袭的影响

Fig 2　The effect of knockdown of *circFOXP1* on the migration and invasion of 6-10B cells

A, Wound healing assay was performed in 6-10B cells of the si-NC and si-circFOXP1 groups. The wound healing rate was significantly decreased in the si-circFOXP1 group compared with the si-NC group ($P < 0.05$). B, Transwell invasion assay was conducted in 6-10B cells of the si-NC and si-circFOXP1 groups. The number of invasive cells was markedly reduced in the si-circFOXP1 group relative to the si-NC group ($P < 0.05$). C, Western blot analysis was performed for the si-NC and si-circFOXP1 groups. Compared with the si-NC group, the protein expression of E-cadherin was significantly upregulated, while N-cadherin was notably downregulated in the si-circFOXP1 group ($P < 0.05$).

表 4　*circFOXP1*沉默抑制6-10B细胞迁移和侵袭（*n*=9）

Table 4　*circFOXP1* silencing inhibits the migration and invasion of 6-10B cells (*n* = 9)

Group	Wound healing rate/%	Number of invasive cells	E-cadherin protein	N-cadherin protein
si-NC	64.26 ± 5.45	97.59 ± 7.82	0.33 ± 0.03	0.57 ± 0.04
si-circFOXP1	26.34 ± 2.47	43.78 ± 4.66	0.78 ± 0.06	0.16 ± 0.02
t	19.012	17.733	20.125	27.504
P	< 0.001	< 0.001	< 0.001	< 0.001

2.4　*circFOXP1*靶向调控miR-4429的表达

StarBase数据库预测显示*circFOXP1*与miR-4429存在互补结合位点（图3）。双萤光素酶报告基因实验结果显示，与miR-NC组比较，miR-4429模拟物与WT-circFOXP1共转染后萤光素酶活性降低（$P<0.05$），而MUT-circFOXP1组萤光素酶活性无明显变化（$P>0.05$）。此外，过表达*circFOXP1*可降低miR-4429表达，而沉默*circFOXP1*可增加miR-4429表达（$P<0.05$）（表5）。

图 3　*circFOXP1*与miR-4429结合序列

Fig 3　The binding sequence of *circFOXP1* and miR-4429

表 5　双萤光素酶报告基因实验结果（*n*=9）

Table 5　Results of dual-luciferase reporter gene assay (*n* = 9)

Group	WT-circFOXP1	MUT-circFOXP1
miR-NC	0.98±0.07	0.99±0.06
miR-4429	0.43±0.04	0.96±0.05
t	20.466	1.152
P	< 0.001	0.266

2.5　上调miR-4429抑制6-10B细胞增殖、迁移和侵袭

如图4和表6所示，与miR-NC组比较，miR-4429组miR-4429表达水平升高，细胞活力、克隆形成数、划痕愈合率、侵袭细胞数和N-cadherin蛋白表达降低，而E-cadherin蛋白表达增加（$P<0.05$）。

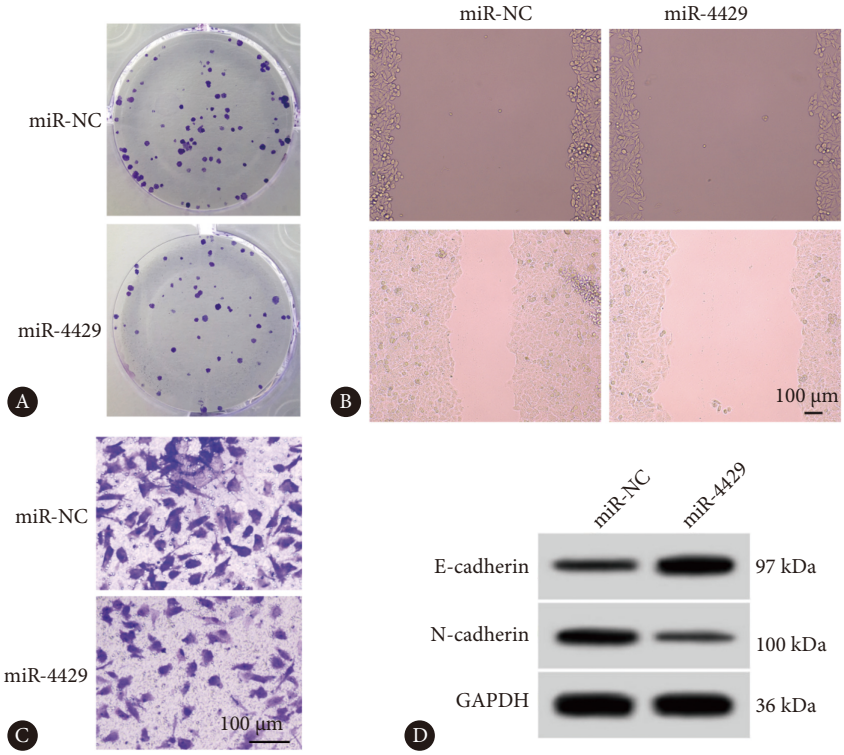

图 4 上调miR-4429抑制6-10B细胞增殖、迁移和侵袭

Fig 4 Upregulation of miR-4429 inhibits proliferation, migration and invasion of 6-10B cells

A, Plate colony formation assay was performed in 6-10B cells of the miR-NC and miR-4429 groups. The number of colonies was significantly decreased in the miR-4429 group compared with the miR-NC group ($P < 0.05$). B, Wound healing assay was conducted in 6-10B cells of the miR-NC and miR-4429 groups. The wound healing rate was markedly reduced in the miR-4429 group relative to the miR-NC group ($P < 0.05$). C, Transwell invasion assay was carried out in 6-10B cells of the miR-NC and miR-4429 groups. The number of invasive cells was significantly lower in the miR-4429 group than in the miR-NC group ($P < 0.05$). D, Western blot analysis was performed for the miR-NC and miR-4429 groups. Compared with the miR-NC group, the protein level of E-cadherin was significantly upregulated in the miR-4429 group ($P < 0.05$).

表 6 上调miR-4429抑制6-10B细胞增殖、迁移和侵袭（*n*=9）

Table 6 Upregulation of miR-4429 inhibits the proliferation, migration and invasion of 6-10B cells (*n* = 9)

Group	miR-4429	OD_{450}	Number of colonies	Wound healing rate/%	Number of invasive cells	E-cadherin protein	N-cadherin protein
miR-NC	1.00 ± 0.00	1.04 ± 0.08	77.85 ± 6.48	65.82 ± 5.55	98.04 ± 8.25	0.32 ± 0.03	0.59 ± 0.05
miR-4429	3.25 ± 0.29	0.68 ± 0.06	42.63 ± 4.51	36.59 ± 3.18	53.68 ± 4.18	0.71 ± 0.07	0.23 ± 0.02
t	23.276	10.800	13.383	13.709	14.389	15.363	20.055
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

2.6 干扰miR-4429逆转*circFOXP1*沉默对6-10B细胞增殖、迁移和侵袭的抑制作用

如图5和表7所示，与si-circFOXP1+anti-miR-NC组比较，si-circFOXP1+anti-miR-4429组miR-4429表达降低，细胞活力、克隆形成数、划痕愈合率、侵袭细胞数和N-cadherin蛋白表达增加，而E-cadherin蛋白表达降低（$P<0.05$）。

3 讨论

鼻咽癌的转移仍然是患者死亡的主要原因，尽管医学取得了重大进展，但鼻咽癌转移的潜在机制尚不清楚[13]。因此，更好地了解其发病和发展背后的机制，以及鉴定鼻咽癌的可靠标记物对于其临床诊断和治疗至关重要。circRNA作为一类特殊的非编码RNA分子，已成为最新的研究热点。它可以作为ceRNA的组成部分来抑制miRNA的活性，从而调节基因转录、翻译和其他功能[14]。本研究探讨了*circFOXP1*在鼻咽癌中的生物功能及其相应的机制，揭示了其作为鼻咽癌诊断生物标志物的潜在临床价值。

研究表明，*circFOXP1*在肝癌组织、血清和细胞中表达上调，*circFOXP1*缺失可抑制肝癌细胞的增殖和侵袭，诱导细胞凋亡，其过表达则显示出相反的趋势[7]。

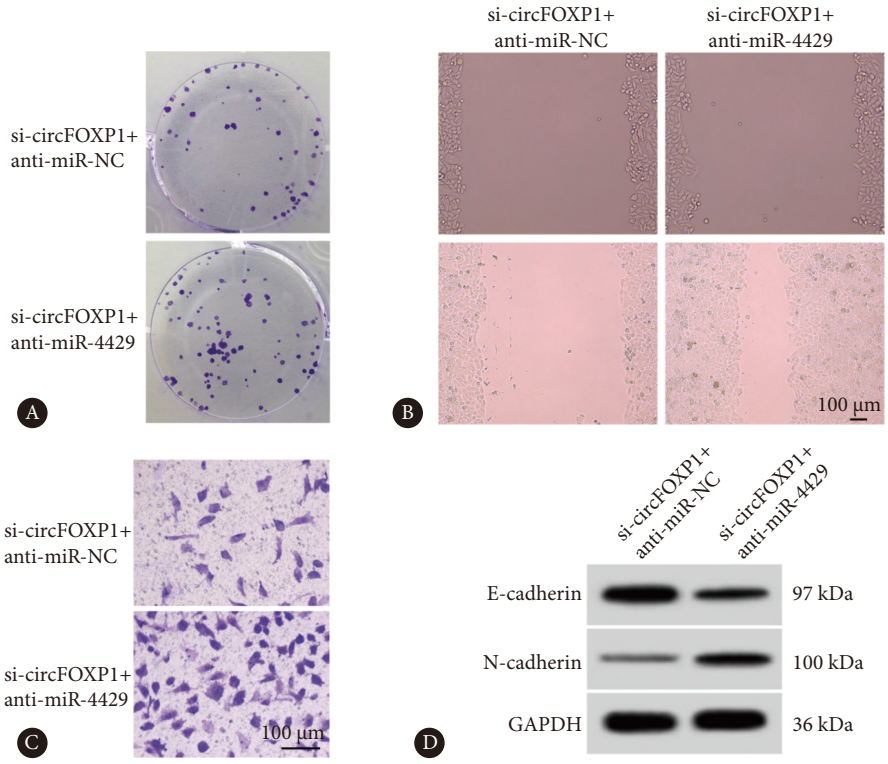

图 5　干扰miR-4429减轻*circFOXP1*沉默对6-10B细胞增殖、迁移和侵袭的作用

Fig 5　The interference of miR-4429 alleviated the effects of *circFOXP1* silencing on the proliferation, migration and invasion of 6-10B cells

A, Plate colony formation assay was performed in 6-10B cells of the si-circFOXP1 + anti-miR-NC and si-circFOXP1 + anti-miR-4429 groups. The number of colonies was significantly increased in the si-circFOXP1 + anti-miR-4429 group compared with the si-circFOXP1 + anti-miR-NC group ($P < 0.05$). B, Wound healing assay was conducted in 6-10B cells of the si-circFOXP1 + anti-miR-NC and si-circFOXP1 + anti-miR-4429 groups. The wound healing rate was significantly elevated in the si-circFOXP1 + anti-miR-4429 group relative to the si-circFOXP1 + anti-miR-NC group ($P < 0.05$). C, Transwell migration and invasion assay was carried out in 6-10B cells of the si-circFOXP1 + anti-miR-NC and si-circFOXP1 + anti-miR-4429 groups. The number of invasive cells was significantly increased in the si-circFOXP1 + anti-miR-4429 group compared with the si-circFOXP1 + anti-miR-NC group ($P < 0.05$). D, Western blot analysis was performed in the si-circFOXP1 + anti-miR-NC and si-circFOXP1 + anti-miR-4429 groups. Compared with the si-circFOXP1 + anti-miR-NC group, the protein expression of N-cadherin was significantly upregulated, while E-cadherin expression was markedly downregulated in the si-circFOXP1 + anti-miR-4429 group ($P < 0.05$).

表 7　敲低*circFOXP1*通过调控miR-4429抑制了6-10B细胞增殖、迁移和侵袭（*n*=9）

Table 7　Down-regulation of *circFOXP1* by regulating miR-4429 inhibits the proliferation, migration and invasion of 6-10B cells (*n* = 9)

Group	miR-4429	OD_{450}	Number of colonies	Wound healing rate/%	Number of invasive cells	E-cadherin protein	N-cadherin protein
si-circFOXP1 + anti-miR-NC	1.00 ± 0.00	0.55 ± 0.05	30.73 ± 3.56	25.58 ± 2.64	41.32 ± 4.35	0.79 ± 0.05	0.14 ± 0.02
si-circFOXP1 + anti-miR-4429	0.36 ± 0.03	0.93 ± 0.08	69.01 ± 5.53	56.47 ± 4.66	86.37 ± 7.56	0.40 ± 0.04	0.49 ± 0.04
t	64.000	12.084	17.461	17.303	15.495	18.272	23.479
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

*circFOXP1*在胆囊癌组织中高表达，具有促进胆囊癌细胞增殖和侵袭的作用[15]。干扰*circFOXP1*靶向调控miR-185-5p，进而削弱肺癌细胞的增殖[9]。这些研究证明*circFOXP1*是一种癌基因，但*circFOXP1*在鼻咽癌中的表达模式仍不清楚。本研究测定了*circFOXP1*在鼻咽癌组织中的表达，发现其表达上调，与LUO等[16]的报道相似。

E-cadherin表达的降低是上皮-间质转化（EMT）和癌症转移过程中的基本事件，而E-cadherin的缺失通常与间充质钙黏蛋白（N-cadherin）的表达增加有关，并且被视为肿瘤细胞获得侵袭性的必要条件。据报道，肿瘤细胞迁移和侵袭行为的发生会引起E-cadherin的缺失和N-cadherin的增加[17]。与前述报告类似，本研究功能测定结果显示，抑制*circFOXP1*表达则抑制了鼻咽癌6-10B细胞的增殖、迁移和侵袭。这首次表明*circFOXP1*与鼻咽癌进展有关。

本研究的qRT-PCR结果首先证实鼻咽癌组织中miR-4429低表达。随后，本研究分析了miR-4429对鼻咽癌6-10B细胞生物学行为的影响。结果表明，miR-4429过

表达可抑制鼻咽癌6-10B细胞的增殖、迁移和侵袭。与本研究的结果相似,根据此前的几项报道,miR-4429在胃癌组织和细胞中下调,其水平与胃癌患者的转移和预后密切相关,过表达miR-4429可抑制胃癌细胞的增殖和迁移潜能[11]。miR-4429靶向*SRXN1*来抑制食管鳞状细胞癌细胞的增殖、迁移、侵袭和体内肿瘤的生长[18]。PAN等[19]的一项研究报告指出,miR-4429在透明细胞肾细胞癌组织和细胞中的表达减少,而miR-4429可以减缓肾透明细胞癌细胞的增殖、迁移和侵袭以及上皮间质转化。

资料显示,circRNA可以通过海绵样吸附miRNA调节其靶基因的表达,这已在包括鼻咽癌在内的多种恶性肿瘤及其进展中得到证实[5-6, 20]。根据生物信息学分析,本研究预测miR-4429是*circFOXP1*潜在的靶基因。通过萤光素酶报告基因分析进一步证实*circFOXP1*直接靶向miR-4429,并负向调控miR-4429表达。此外,下调miR-4429可缓解*circFOXP1*沉默对鼻咽癌细胞增殖、迁移和侵袭的抑制作用。提示*circFOXP1*通过靶向miR-4429调控鼻咽癌细胞的生物学行为。

总之,本研究数据清楚地表明,*circFOXP1*是鼻咽癌肿瘤发生和侵袭性进展的新型驱动力,*circFOXP1*通过靶向miR-4429加速鼻咽癌进程。这项研究提高了对鼻咽癌发病机制的理解,*circFOXP1*和miR-4429可能成为鼻咽癌的治疗靶点。

* * *

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