miR-146a在头颈肿瘤中的作用及研究进展

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摘要 微小RNA(microRNA, miRNA)是一种普遍表达于真核生物的RNA分子, 没有编译蛋白质的功能, 是非编码RNA的一员。近年来, 愈来愈多的研究证明miRNA参与调控肿瘤细胞的增殖、凋亡, 肿瘤组织血管的形成, 肿瘤的转移、免疫逃逸等。miR-146a是miRNA家族中的其中一员, 其在肿瘤组织中的研究成果日益增多。该文就miR-146a在头颈肿瘤中的作用及研究进展作一综述。

关键词 miR-146a; 头颈肿瘤

The Role and Research Progress of miR-146a in Head and Neck Tumors

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Abstract MicroRNA (miRNA) is a kind of RNA molecule which is widely expressed in eukaryotes. It has no function of compiling proteins and is a member of non-coding RNA. In recent years, more and more studies have proved that miRNA is involved in the regulation of tumor cell proliferation, apoptosis, tumor tissue vascular formation, tumor metastasis, immune escape and so on. miR-146a is one member of the miRNA family, and its research results in tumor tissues are increasing day by day. In this paper, the role and research progress of miR-146a in head and neck tumors are reviewed.

Keywords miR-146a; head and neck tumor

头颈肿瘤包括头部和颈部的非黑色素瘤皮肤癌、上消化道黏膜表面的口腔、咽、喉、副鼻窦、唾液腺恶性肿瘤、甲状腺肿瘤等, 临床资料分析显示, 头颈肿瘤大多数病理类型是鳞状细胞肿瘤[1]。头颈鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC)在全世界范围内每年约有60万新发病例, 常表现为局部侵犯性疾病[2-3]。HNSCC的侵袭、迁移和转移能力强, 造成临床上治疗难度加大, 患者预后较差。在过去的几十年中, HNSCC在临床治疗策略、技术上已有了许多创新, 但总的5年存活率仍然只有大约50%, 发生转移后5年存活率则低于30%[4]。已经有研究证实, miRNA在各类肿瘤中都有一定作用, 所以, 基于miRNA研究HNSCC发展的分子机制和筛选准确的生物分子标记是有意义的。

1 miRNA和miR-146a概述

全基因组中参与编码蛋白质的基因比例随着生物复杂程度的增加而降低, 而在哺乳动物中超过

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97%的转录产物是非编码RNA[5]。miRNA是最近几年发现的一类由21~25个核苷酸构成的小的非编码RNA, 它们的作用是通过诱导抑制靶基因的翻译或转录来降低靶基因的表达[6-8]。在人类细胞核内, 初级miRNA是编码miRNA的相干基因通过RNA聚合酶II或III转录产生的。然后, 微处理复合物Drosha-DGCR8将初级miRNA裂解成含有发夹结构的前体miRNA[9-10]。紧接着, 前体miRNA从细胞核运动到胞质中, RNase Dicer酶将前体miRNA裂解为约22 nt的成熟miRNA, 这时的miRNA还处于双链形态。最后, 双链miRNA被转载进AGo2(Argonaute 2)蛋白中, 形成RNA诱导沉默复合体(RNA-induced silencing complex, RISC)[11]。估计RISC是与目标基因的3′非翻译区(3′-untranslated region, 3′-UTR)的不完全互补结合来调控基因的表达[12-14]。

目前, 已经有研究显示, 肿瘤细胞的分化、凋亡和增殖、侵袭和转移等过程与miRNA调控密切相关[15-19], 这表明miRNA作为一种重要的转录后调控基因在肿瘤发生、发展中发挥着关键作用。miR-146是miRNA家族中的一员, 人类的miR-146有两个亚型, miR-146a和miR-146b, 前者位于人第5号染色体*LOC 285628*基因上[20], 后者位于人类染色体中10q24-26上[21]。这两者在结构上并无太大差别, 它们仅在成熟序列的3′末端存在两个核苷酸的不同, 而miR-146这个家族中研究最多的成员是miR-146a[22]。其不仅参与正常组织的各种生理活动, 而且在多种实体肿瘤发生、发展阶段中, miR-146a的表达会发生上调或者下调[23-24]。

2 miR-146a与头颈肿瘤

与HNSCC相关的危险因素有烟草、酒精, 还有槟榔和人乳头瘤病毒感染, 后两个危险因素可能是近年来年轻女性新发病率增长的原因[25]。有一份关于厄瓜多尔混血儿的头颈肿瘤病例对照研究发现, 相比于正常组织, miR-146a在喉、口咽、咽和口腔肿瘤中表达显著上调; 并且它在HPV^+患者中表达下调, 在HPV^-患者中表达上调[26]; 此外, 研究还表明miR-146a对HNSCC的肿瘤分期(TNM2-4)也有一定的指导作用[26]。由此, 我们推测, miR-146a的表达对HNSCC有一定的诊断价值。

2.1 miR-146a与鼻咽癌

鼻咽癌(nasopharyngeal carcinoma, NPC)是好发于咽隐窝和顶后壁所在区域, 起源于生被覆上皮和腺上皮的恶性肿瘤。虽然, 世界范围内的鼻咽癌发病率较低, 但我国南方地区和亚洲东南部是高发区[27]。NPC男女发病比例为2:1~3:1[28]。现在临床上NPC治疗方案主要是放疗, 它能较好控制肿瘤的进展。其中, 由于鼻咽部周围丰富的淋巴组织和解剖位置特殊, 其远处转移和高复发率是鼻咽癌生存率不高的主要原因。Lung等[29]发现, 鼻咽癌组织标本中3种成熟的miRNA(miR-146a、miR-146a*a和miR-146a*c)均表达上调, 与EB病毒编码的潜伏膜蛋白1(latent membrane protein 1, LMP1)呈正相关, 而且都可与RNA诱导的沉默复合物的关键分子——内源性AGo2蛋白形成复合物, 表明3种成熟的miR-146a都具有功能活性, 可能通过与LMP1的相互作用的方式调控鼻咽癌的进展。多项研究表明, miR-146a表达水平受单核苷酸多态性(single nucleotide polymorphism, SNP)调控, 该G/C SNP(*rs2910164*)位于miR-146a的前体区, 若位点发生突变可引起miRNA茎环结构中出现C:U的错配, 从而影响前体miR-146a到成熟miR-146a的表达[30-33]。Huang等[30]分析miR-146a基因多态性与中国南部鼻咽癌易患风险关系发现, *rs2910164* C等位基因或CC基因型与中国南部人群鼻咽癌的发病风险密切相关, 其增加了鼻咽癌的发病风险。此外, Hao等[31]的Meta分析也表明, *rs2910164* C等位基因增加鼻咽癌的发病风险。然而, Zhang等[32]的Meta分析和Wu等[33]的测序研究发现, *rs2910164* C等位基因或CC基因型与鼻咽癌发病风险呈负相关。虽然, 上述研究的结果是相互矛盾的, 可能是由于样本量、研究群体(种族、年龄、性别)的不同造成了一定的偏倚, 但都表明miR-146a与鼻咽癌相关, 具体的作用形式和机制, 还需要大样本的分析, 甚至细胞功能实验、动物模型以及调控通路研究来验证。

2.2 miR-146a与喉癌

喉癌是常见的HNSCC之一, 95%~98%的病理组织类型是鳞状细胞癌(laryngeal squamous cell carcinoma, LSCC), 主要症状为呼吸困难、声嘶、颈部淋巴结转移、吞咽困难等, LSCC后期严重影响患者的呼吸、吞咽和发音功能, 患者生活质量极差[34]。肖文杰[35]研究发现, miR-146a在喉鳞状细胞癌组织中的表达水平明显高于相应的癌旁非肿瘤组织; 在LSCC细胞中, 抑制乳腺癌转移抑制基因1(breast

cancer metastasis suppressor gene 1, *BRMS1*)的表达降低, miR-146a表达水平升高, 这项研究提示, miR-146a和*BRMS1*都参与了LSCC的发生、发展过程。miR-146a在此可能起到了促癌作用, 其中*BRMS1*有可能直接或间接下调miR-146a的表达。林丹等[36]首次进行了miR-146a前体区基因多态性位 点 与LSCC患病风险的关联性强度分析, 发现无论在何种临床分期和病理分级, miR-146a *rs2910164* GC/CC基因型均增加个体罹患LSCC的风险, 而与LSCC的进展无关联, 这表明, *rs2910164*可以作为预测LSCC发生的潜在生物标志物。

2.3 miR-146a与甲状腺癌

甲状腺癌是女性头颈肿瘤中最为常见的恶性肿瘤, 其在女性恶性肿瘤中排第5位[2]。根据相关统计分析, 1992~2010年, 美国甲状腺癌的发病率以每年5.3%的幅度增长[37]。甲状腺癌的死亡率不高, 但是有的高分化甲状腺肿瘤有不确定的恶性潜能, 需要引起我们的重视。一些研究发现, miR-146a在原发性间变性甲状腺癌[38]、乳头状甲状腺癌(papillary thyroid carcinoma, PTC)[39-43]、滤泡性甲状腺癌[44]组织中过表达。多项研究发现, miR-146a的表达水平与PTC的淋巴结转移, 肿瘤分期密切相关, 且都表明了miR-146a促进了甲状腺肿瘤的增殖、侵袭、迁移, 具有促癌作用[40,42-43]。miR-146a不仅在肿瘤组织与癌旁组织(正常组织)中表达量不同, 而且可以区分有恶性潜能的甲状腺肿瘤。Lassalle等[44]研究发现, 一组miRNA(包括miR-146a)有助于“不确定恶性潜能的甲状腺肿瘤”(thyroid tumors of uncertain malignant potential, TT-UMP)的诊断。甲状腺癌术后的复发检测关键的生物标志物是血清甲状腺球蛋白(thyroglobulin, Tg)。Tg是甲状腺细胞合成并释放的一种大分子糖蛋白, 仅在正常的甲状腺细胞和分化型甲状腺癌细胞中产生。Tg水平还受到抗Tg自身抗体(anti-thyroglobulin antibodies, TgAb)水平的影响, TgAb存在会降低血清当中的Tg检测值, 从而影响用Tg来监测甲状腺癌复发的准确性。所以其特异性因为抗Tg自身抗体和残留的甲状腺组织受到限制。Rosignolo等[45]对在乳头状甲状腺癌术后随访中发现, 血清Tg水平持续低于1 ng/mL或者持续存在局部肿瘤病灶或有远处转移的患者的血清中miR-146a持续升高。这表明, miR-146a可以作为PTC患者术后监测的血清生物标志物, 尤其是在Tg检测结果不明确的情况下。

2.4 miR-146a与口腔癌

口腔癌可以发生于口腔或口咽区域的任意部位, 大多数发生于舌部和口腔底部, 多以口腔鳞癌(oral squamous cell carcinoma, OSCC)为主。近几年来, 其发病率逐年上升[46]。研究发现, miR-146a在口腔鳞状细胞癌组织中的表达是明显高于健康口腔黏膜组织或癌旁组织[47-50]。在此基础上, Hung等[47]发现, *IRAK 1*、*TRAF 6*和*NUMB*是miR-146a在口腔鳞癌细胞中的作用靶点, 通过下调*IRAK 1*、*TRAF 6*和*NUMB*的表达来促进OSCC的增殖、侵袭和转移。此外, Shia等[51]研究发现, 转录因子*Sox2*是miR-146a作用靶点, 沉默*Sox2*使OSCC的miR-146a过表达从而抑制癌细胞的增殖、侵袭和转移。综合目前研究可知, miR-146a在OSCC中有双相调控, 我们需要分析下游的调控靶点, 进一步明确miR-146a在OSCC中的诊断价值。

3 展望

综上所述, miR-146a在头颈肿瘤的转化、克隆性增生、演进及预后中起着重要作用。但是, 目前miR-146a在头颈肿瘤作用机制研究不多, 尤其是在下咽癌、喉癌、鼻咽癌中的机制研究还很欠缺, 在口腔鳞癌、甲状腺癌中作用机制的研究也是刚刚起步。随着越来越多的MicroRNAs for Early研究者投身到miR-146a与头颈肿瘤相关作用研究中, 我们相信未来miR-146a在头颈肿瘤中发挥的作用及其机制都可以被揭示出来, 以此研究出新型靶向药物, 对头颈肿瘤的早期临床诊断、治疗提供新方向。

参考文献 (References)

1 William ML, Snehal GP, Brian OS, Margaret SB, John AR, Jocelyn CM, *et al*. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(2): 122-37.

2 Rebecca LS, Kimberly DM, Ahmedin J. Cancer statistics, 2016. CA Cancer J Clin 2016; 66(1): 7-30.

3 Jacques F, Isabelle S, Rajesh D, Sultan E, Colin M, Marise R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): 359-86.

4 Ruth T, Jan K, Linda R, Elaine S, Martina S, Jana S, *et al*. Demographic and risk factors in patients with head and neck tumors. J Med Virol 2009; 81(5): 878-87.

5 Svetlana AS, Nikolay AS. The mammalian transcriptome and the function of non-coding DNA sequences. Genome Biol 2004;

5(4): 105.
6 He L, Hannon GJ. Correction: MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5(8): 631.
7 Victor A, Rosalind CL, Ann L, Peter TW, David J. MicroRNAs and other tiny endogenous RNAs in *C. elegans*. Curr Biol 2003; 13(10): 807-18.
8 Haruhiko S, Mikiko CS. On the road to reading the RNA-interference code. Nature 2009; 457(7228): 396-404.
9 Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, *et al*. The nuclear RNase III Drosha initiates microRNA processing. Nature 2003; 425(6956): 415-9.
10 Lee Y, Jeon K, Lee JT, Kim S, Kim VN. MicroRNA maturation: stepwise processing and subcellular localization. EMBO J 2002; 21(17): 4663-70.
11 Gunter M, Markus L, Agnieszka P, Yair D, Grace T, Thomas T. Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs. Mol Cell 2004; 15(2): 185-97.
12 Anastasia K, Angela R, Sumedha DJ. Functional siRNAs and miRNAs exhibit strand bias. Cell 2003; 115(2): 209-16.
13 David PB. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116(2): 281-97.
14 Benjamin PL, Christopher BB, David PB. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005; 120(1): 15-20.
15 Eis PS, Tam W, Sun L, Chadburn A, Li Z, Gomez MF, *et al*. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci USA 2005; 102(10): 3627-32.
16 Jennifer AC, Anna MK, Kenneth SK. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res 2005; 65(14): 6029-33.
17 Junichi T, Hiroyuki K, Kiyoshi Y, Shuta T, Hirotaka O, Hideki E, *et al*. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Res 2004; 64(11): 3753-6.
18 Yu SL, Chen HY, Chang GC, Chen CY, Chen HW, Singh S, *et al*. MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell 2008; 13(1): 48-57.
19 Zhu S, Wu H, Wu F, Nie D, Sheng S, Mo YY. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res 2008; 18(3): 350-9.
20 Rupninder S, Jessica R, Monica DA, Jason IH, Katherine AH, Melissa AT. Overexpression of miR-146a in basal-like breast cancer cells confers enhanced tumorigenic potential in association with altered p53 status. Carcinogenesis 2014; 35(11): 2567-75.
21 Tomoyuki N, Shigeru M, Atsuko O, Megumi H, Keiichiro N, Mitsuo O, *et al*. Expression of microRNA-146 in rheumatoid arthritis synovial tissue. Arthritis Rheum 2008; 58(5): 1284-92.
22 张丽丹, 曾菁莘, 刘炜钰, 林玲, 罗权. miR-146a在银屑病发病机制中的研究进展. 皮肤性病诊疗学杂志(Zhang Lidan, Zeng Jingxin, Liu Weiyu, Lin Ling, Luo Quan. Research progress of mir-146a in the pathogenesis of psoriasis. Journal of Diagnosis and Therapy on Dermato-venereology) 2018; 25(2): 120-2.
23 Kumaraswamy E, Wendt KL, Augustine LA, Stecklein SR, Sibala EC, Li D, *et al*. BRCA1 regulation of epidermal growth factor receptor (EGFR) expression in human breast cancer cells involves microRNA-146a and is critical for its tumor suppressor function. Oncogene 2015; 34(33): 4333-46.
24 Li Y, Xu Y, Yu C, Zuo W. Associations of miR-146a and miR-146b expression and breast cancer in very young women. Cancer Biomark 2015; 15(6): 881-7.
25 Xie C, Ji N, Tang Z, Li J, Chen Q. The role of extracellular vesicles from different origin in the microenvironment of head and neck cancers. Mol Cancer 2019; 18(1): 83.
26 Salazar-Ruales C, Arguello JV, López-Cortés A, Cabrera-Andrade A, García-Cárdenas JM, Guevara-Ramírez P, *et al*. Salivary micrornas for early detection of head and neck squamous cell carcinoma: a case-control study in the high altitude mestizo Ecuadorian population. Biomed Res Int 2018; 2018: 9792730.
27 邓伟, 黄天壬, 陈万青, 张思维, 郑荣寿, 利基林. 中国2003-2007年鼻咽癌发病与死亡分析. 肿瘤(Deng Wei, Huang Tianreng, Chen Wanqing, Zhang Siwei, Zheng Rongshou, Li Jilin. Analysis of the incidence and mortality of nasopharyngeal carcinoma in China between 2003 and 2007. Tumor) 2012; 32(3): 189-93.
28 Xie SH, Yu IT, Tse LA, Mang OW, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983-2008: suggestion of a potential protective role of oestrogen. Eur J Cancer 2013; 49: 150-5.
29 Lung RW, Wang X, Tong JH, Chau SL, Lau KM, Cheng SH, *et al*. A single nucleotide polymorphism in microRNA-146a is associated with the risk for nasopharyngeal carcinoma. Mol Carcinog 2013; 52 Suppl 1: 28-38.
30 Huang GL, Chen ML, Li YZ, Lu Y, Pu XX, He YX, *et al*. Association of miR-146a gene polymorphism with risk of nasopharyngeal carcinoma in the central-southern Chinese population. J Hum Genet 2014; 59(3): 141-4.
31 Xia H, Lingzi X, Ruoyi Q, Xianglin Y, Min J, Baosen Z. Association between miR-146a rs2910164 polymorphism and specific cancer susceptibility: an updated meta-analysis. Fam Cancer 2018; 17(3): 459-68.
32 Zhang S, Hu F, Liang H, Liu Y, Yang J, Zhou W. Association between a miRNA-146a polymorphism and susceptibility to head and neck squamous cell carcinoma in Chinese patients: A meta-analysis of 8 case-control studies. PLoS One 2017; 12(10): e0186609.
33 Wu MY, Huang SJ, Yang F, Qin XT, Liu D, Ding Y, *et al*. Detection of nasopharyngeal carcinoma susceptibility with single nucleotide polymorphism analysis using next-generation sequencing technology. Oncotarget 2017; 8(32): 52708-23.
34 Elisabeth R, Gerhard D, Heiko B, Andreas D, Heribert R. Effects of tumour stage, comorbidity and therapy on survival of laryngeal cancer patients: a systematic review and a meta-analysis. Eur Arch Otorhinolaryngol 2011; 268(2): 165-79.
35 肖文杰. miR-146a在喉癌中的表达及其与BRMS1相关性的研究. 广东医学院(Xiao Wenjie. the expression of miR-146a in laryngeal cancer and the correlation with BRMS1. Guangdong Medical College), 2015.
36 林丹, 董伟达, 陆美萍, 邢光前, 董佳迪, 张伟强. MicroRNA-146a前体区基因多态性与江苏地区汉族人群喉癌遗传易感性的关联性分析. 山东大学耳鼻喉眼学报(Lin Dan, Dong Weida, Lu Meiping, Xing Guangqian, Dong Jiadi, Zhang Weiqiang. The association between rs2910164 G>C polymorphism in pre-microRNA-146a and laryngeal cancer in Jiangsu Han population.

Journal of Otolaryngology and ophthalmology of Shandong University) 2014; 28(2): 46-50.

37 Angelina M, Darrin VB, Jane RS, David G. The effects of race and ethnicity on thyroid cancer incidence. JAMA Otolaryngol Head Neck Surg 2015; 141(4): 319-23.

38 Francesco P, Elvira C, Stefano M, Alessio I, Nunzio P, Domenico L, *et al*. Nuclear factor-{kappa}B contributes to anaplastic thyroid carcinomas through up-regulation of miR-146a. J Clin Endocrinol Metab 2010; 95(3): 1421-30.

39 Krystian J, Joanna B, Jaroslaw J, Sandya L, Janusz P, Kazimierz AW, *et al*. Thyroid hormone receptor beta (THRB) is a major target gene for microRNAs deregulated in papillary thyroid carcinoma (PTC). J Clin Endocrinol Metab 2011; 96(3): 546-53.

40 Mei S, Sheng F, Weiwei L, Chengqian L, Luan W, Fang W, *et al*. Associations of miR-146a and miR-146b expression and clinical characteristics in papillary thyroid carcinoma. Cancer Biomark 2015; 15(1): 33-40.

41 Agnieszka Anna C, Anna W, Anna K, Marta K, Elwira B-Z, Łukasz K, *et al*. Family of microRNA-146 regulates RARβ in papillary thyroid carcinoma. PLoS One 2016; 11(3): e0151968.

42 Qiu Z, Li H, Wang J, Sun C. miR-146a and miR-146b in the diagnosis and prognosis of papillary thyroid carcinoma. Oncol Rep 2017; 38(5): 2735-40.

43 迟庆霞, 王颜刚, 赵文娟, 余霄龙, 王萍, 刘鑫, 等. 甲状腺乳头状癌组织及外周血中miR-146a含量变化. 中华内分泌外科杂志(Chi Qingxia, Wang Yangang, Zhao Wenjuan, Yu Xiaolong, Wang Ping, Liu Xin, *et al*. The change of miR-146a in carcinoma tissues and peripheral blood of patients with papillary thyroid carcinoma. Chinese Journal of Endocrine Surgery) 2013; 7(1): 56-9.

44 Ma W, Zhao X, Liang L, Wang G, Li Y, Miao X, Zhao Y. miR-146a and miR-146b promote proliferation, migration and invasion of follicular thyroid carcinoma via inhibition of ST8SIA4. Oncotarget 2017; 8(17): 28028-41.

45 Francesca R, Marialuisa S, Laura G, Diego R, Valeria P, Marco B, *et al*. Identification of thyroid-associated serum microRNA profiles and their potential use in thyroid cancer follow-up. J Endocr Soc 2017; 1(1): 3-13.

46 Christina F, Daniel D, Amanda P, Hannah H, Maziar M-L, Michael FM, *et al*. The global burden of cancer 2013. JAMA Oncol 2015; 1(4): 505-27.

47 Hung PS1, Liu CJ, Chou CS, Kao SY, Yang CC, Chang KW, *et al*. miR-146a enhances the oncogenicity of oral carcinoma by concomitant targeting of the IRAK1, TRAF6 and NUMB genes. PLoS One 2013; 8(11): e79926.

48 Kao YY, Tu HF, Kao SY, Chang KW, Lin SC. The increase of oncogenic miRNA expression in tongue carcinogenesis of a mouse model. Oral Oncol 2015; 51(12): 1103-12.

49 Davide BG, Luca M, Andrea G, Achille T, Claudio M, Francesca C, *et al*. A Noninvasive test for microRNA expression in oral squamous cell carcinoma. Int J Mol Sci 2018; 19(6): 1789.

50 王丽萍, 郭雪琪, 闫勇勇, 查骏, 陈伟鸿, 魏永祥, 等. miR-146a在口腔鳞癌组织及细胞中的表达及功能研究. 口腔医学研究(Wang Liping, Guo Xueqi, Yan Yongyong, Cha Jun, Chen Weihong, Wei Yongxiang, *et al*. Effect and functional role of miR-146a in oral squamous cell carcinoma tissue and cell lines. Journal of Oral Science Research) 2017; 33(11): 1204-8.

51 Shi Z, Johnson JJ, Jiang R, Liu Y, Stack MS. Decrease of miR-146a is associated with the aggressiveness of human oral squamous cell carcinoma. Arch Oral Biol 2015; 60(9): 1416-27.