

微小RNA-143/145基因簇在口腔鳞状细胞癌细胞信号通路调控中作用的研究进展

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[摘要] 口腔鳞状细胞癌(OSCC)是口腔颌面部最常见的恶性肿瘤,由于缺乏特异性治疗手段,传统的手术切除仍是主要的治疗策略,但随之而来的口腔颌面部缺损对患者的生活质量造成了严重影响,因此阐明调控OSCC发生发展的分子机制愈显必要。越来越多的报道提示微小RNA(miRNA)-143和miRNA-145在OSCC中异常表达,并深入参与其发生演进。研究miRNA-143和miRNA-145在OSCC中的表达及靶基因调控作用有助于进一步阐明其分子机制,明确二者作为生物标志物和分子靶标的价值,从而为OSCC临床诊疗提供新思路。

[关键词] 微小RNA-143; 微小RNA-145; 口腔鳞状细胞癌; 信号通路; 靶基因

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Research progress in the regulatory role of microRNA-143/145 gene cluster in signaling pathways of oral squamous cell carcinoma

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[Abstract] Oral squamous cell carcinoma (OSCC) is the most prevalent malignant neoplasm in the oral and maxillofacial region. Traditional surgical excision remains the primary treatment because of the lack of specific therapeutic approaches. However, the resultant oral and maxillofacial defects severely impact patients' quality of life. Therefore, elucidating the molecular mechanisms regulating OSCC development is crucial. microRNA (miRNA)-143 and miRNA-145 are aberrantly expressed in OSCC and significantly participate in its pathogenesis. Studying the expression and target gene regulation of miRNA-143 and miRNA-145 in OSCC may help clarify its molecular mechanisms, confirm their value as biomarkers and molecular targets, and provide new insights for clinical diagnosis and treatment.

[Key words] microRNA-143; microRNA-145; oral squamous cell carcinoma; signaling pathway; target gene

口腔癌主要起源于口腔黏膜组织,是全球常见的恶性肿瘤之一,发病率逐年上升^[1-3]。口腔鳞

状细胞癌(oral squamous cell carcinoma, OSCC)是口腔癌中最常见的类型,占比约90%,常见于舌、唇、颊等部位。OSCC的主要特点包括强烈的局部侵袭性和较高的颈部淋巴结转移率,这不仅严重影响患者的身心健康和生活质量,也带来了巨大的社会经济负担^[4]。目前,由于缺乏有效的治

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疗手段，OSCC的5年生存率较低^[5-6]。尽管OSCC的具体发病机制尚未完全明了，但研究表明多条信号通路、多种下游蛋白以及众多微小RNA（micro RNA，miRNA）与其发病过程密切相关，这为治疗提供了潜在的靶点。为了更好地理解OSCC的复杂发病机制，进一步研究与OSCC发展相关的miRNA及其调控的靶基因显得尤为重要。本文旨在综述miR-143/145基因簇在OSCC发展中对相关靶基因的调控作用，以期为未来的研究和治疗提供参考。

1 miRNA的合成与功能调控

miRNA是一类广泛存在于真核细胞中的单链非编码RNA，其长度通常在18~25个核苷酸之间。miR的合成开始于编码其DNA的转录，形成初级miRNA（pri-miRNA）。这些pri-miRNA随后由Rnase III家族成员Drosha剪切成约70个核苷酸长、具有茎环结构的前体miRNA（pre-miRNA）。这些pre-miRNA在细胞核内，依赖RanGTP/Exportin5转运至细胞质，在那里被另一RNase III家族成员Dicer进一步剪切成约22个核苷酸长的双链miRNA。最终，这些双链miRNA由解旋酶处理成成熟的miRNA^[7-10]。miRNA的简要合成过程见图1。

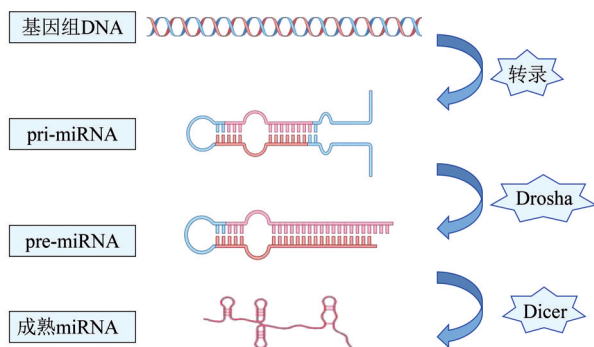


图1 miRNA的合成

Fig 1 The synthesis of miRNA

miRNA通过与靶基因信使RNA（messenger RNA，mRNA）的3'非编码区内的miRNA反应元件不完全互补结合，抑制其翻译或诱导其降解，从而下调相关蛋白的表达。与此同时，miRNA的功能发挥受到多种上游因子的调控，主要包括转录因子、外部信号通路和竞争性内源RNA分子（competing endogenous RNA，ceRNA）。转录因子骨髓细胞瘤癌基因编码蛋白（myelocytomatosis oncogene gene，Myc）通过结合miRNA编码基因

上游的顺式作用元件来调节miRNA的转录，从而上调miRNA表达，促进细胞增殖^[11]。外部信号如生长因子和细胞因子，也可以通过激活特定信号通路来影响miRNA的合成^[12]。ceRNA分子，如长链非编码RNA（long non-coding RNA，lncRNA）和环状RNA（circle RNA，circRNA），可与靶基因mRNA竞争结合miRNA，从而调节miRNA的有效浓度，影响下游基因的表达^[13]。这些调控机制确保miRNA的表达能够及时响应细胞环境的变化，从而在细胞发育、细胞免疫及细胞周期调控等多种生物过程中发挥作用^[14]。例如，miR-21通过抑制抑癌基因同源性磷酸酶张力蛋白（phosphatase and tensin homolog，PTEN）和程序性细胞死亡因子4（programmed cell death 4，PDCD4），促进细胞增殖和抑制细胞凋亡^[15-16]。miR-155通过调控免疫细胞功能，影响炎症反应和自身免疫疾病的进展^[17-18]。miR-34a通过靶向细胞周期蛋白D1（cyclin D1，CCND1）抑制细胞进入S期，进而影响细胞增殖^[19]。miRNA的功能调控见图2。

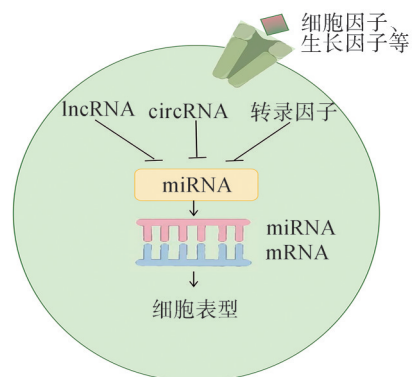


图2 miRNA的功能调控

Fig 2 Regulation of miRNA function

2 miR-143/145基因簇与OSCC

2.1 miR-143/145基因簇概述

miR-143和miR-145的编码基因位于人类5号染色体长臂3区3带（5q33）。由于它们相距不超过2 kb，共享一个启动子，常同步表达，因此被称为miR-143/145基因簇。Michael等^[20]在2003年报道miR-143和miR-145在结直肠癌组织中低表达。此后研究发现，miR-143、miR-145在多种恶性肿瘤中差异表达，普遍具有抑制肿瘤发生发展的作用。此外，miR-143和miR-145的表达水平与多种肿瘤的预后密切相关，这为临床提供了重要参考^[21-23]。

2.2 miR-143、miR-145在OSCC中的差异表达

2.2.1 miR-143的差异表达

Mesgarzadeh等^[24]通过定量逆转录聚合酶链反应 (quantitative reverse transcription polymerase chain reaction, qRT-PCR) 检测发现, miR-143在晚期OSCC中表达下调, 并与转移状态相关。Sun等^[25]的研究显示, miR-143在OSCC组织中的表达显著低于正常口腔组织。

miR-143在OSCC细胞株中的过表达抑制了细胞增殖, 促进凋亡, 并导致细胞周期停滞在G1期。Yu等^[26]的OSCC动物模型研究也发现, miR-143在癌组织中显著下调。

这些研究表明, miR-143在OSCC进展中通常下调, 可能具有抑癌作用。

2.2.2 miR-145的差异表达

Singh等^[27]的研究显示, miR-145在OSCC组织中的表达显著低于正常口腔黏膜组织, 并与肿瘤大小、淋巴结状态、病理分期及临床分期相关。Wang等^[28]发现miR-145在原发和复发OSCC组织中的表达均降低, 且化疗耐药的OSCC组织中miR-145表达下调。刘岚等^[29]的研究表明, OSCC患者血清中miR-145表达低于正常对照组, 并与颈部淋巴结转移、肿瘤分化程度和TNM分期有关。Gao等^[30]和邵渊等^[31]的研究也支持miR-145在OSCC中的低表达, 提示其可能是潜在的抑癌因子, 表达下调可能减少肿瘤抑制作用, 促进OSCC发生。miR-143、miR-145在OSCC中的差异表达总结见表1。

表 1 miR-143、miR-145在OSCC中的差异表达

Tab 1 The differential expression of miR-143 and miR-145 in OSCC

研究者	时间/年	来源	方法	miRNA	表达
Yu等 ^[26]	2009	3例OSCC动物模型和3例正常动物模型	qRT-PCR	miR-143、miR-145	下调
Gao等 ^[30]	2013	62例OSCC组织样本	qRT-PCR	miR-145	下调
邵渊等 ^[31]	2014	口腔癌细胞株CAL27	qRT-PCR	miR-145	下调
Wang等 ^[28]	2016	暴露于槟榔碱的口腔上皮细胞株 (AOE)	qRT-PCR	miR-145	下调
Sun等 ^[25]	2017	15例OSCC组织样本和15例正常口腔黏膜组织样本	qRT-PCR	miR-143	下调
Mesgarzadeh等 ^[24]	2019	口腔癌细胞株HN-5	qRT-PCR	miR-143	下调
Singh等 ^[27]	2023	50例OSCC组织样本和20例正常口腔黏膜组织样本	qRT-PCR	miR-145	下调
刘岚等 ^[29]	2024	102例OSCC组织样本和86例正常口腔黏膜组织样本	qPCR	miR-145	下调

2.3 miR-143、miR-145在OSCC中对下游靶基因的调控

2.3.1 miR-143的下游靶基因调控

Manikandan等^[32]研究表明, miR-143通过直接靶向双微体同源基因2 (mouse double minute 2, MDM2) 影响肿瘤蛋白p53的稳定性和活性, 其下调导致p53功能减弱, 进而促进OSCC发展。Xu等^[33]发现, miR-143可抑制OSCC细胞的迁移和侵袭, 且其表达与白细胞分化抗原44 (cluster of differentiation 44, CD44) 呈负相关。Yu等^[34]研究显示, 黑素瘤抗原家族A9 (melanoma-associated antigen family member A9, MAGEA9) 在OSCC组织中的表达明显升高, 抑制miR-143-3p可上调MAGEA9的表达, miR-143-3p模拟物则下调MAGEA9, 二者在OSCC中呈负相关。Bufalino等^[35]观察到OSCC细胞中miR-143和miR-145的下调与激活素A (activin A, ACVA) 水平呈负相关, 过表达miR-143、miR-145显著可下调ACVA。

2.3.2 miR-145的下游靶基因调控

Shao等^[36]发现, miR-145可抑制OSCC细胞的

增殖和集落形成能力, 并诱导G1期停滞和凋亡。过表达miR-145可降低骨髓细胞瘤癌基因编码蛋白 (myelocytomatosis oncogene gene, c-Myc) 和细胞周期蛋白依赖性激酶6 (cyclin dependent kinase 6, CDK6) 的表达水平。冯素亚等^[37]的研究表明, OSCC中同源形成素样蛋白2 (Formin like 2, FMNL2) 高表达, 并且Notch信号通路显著激活, 过表达miR-145-5p或沉默FMNL2能有效抑制Notch信号通路, 同时抑制OSCC细胞的增殖和侵袭能力, 促进细胞的凋亡。郭芳等^[38]通过生物信息学和双荧光素酶报告基因分析, 确认了CDK6是miR-145的靶基因。陆伟等^[39]研究表明, 核糖体蛋白S6激酶 (riboso-mal protein S6 kinase B1, RPS6KB1) 在OSCC中表达上调, 双荧光素酶报告基因分析明确了RPS6-KB1是miR-145的靶基因, miR-145可通过靶向RPS6KB1调控OSCC细胞的侵袭和迁移能力。赵微等^[40]发现, miR-145-5p可通过靶向神经母细胞瘤鼠肉瘤同系物 (neuroblastoma ratsarcoma homolog, NRAS), 阻断丝裂原活化蛋白激酶 (mitogen activated protein kinase, MAPK) 信号通

路,进而抑制OSCC细胞增殖并诱导凋亡。miR-

143、miR-145对下游靶基因的调控总结见图3。

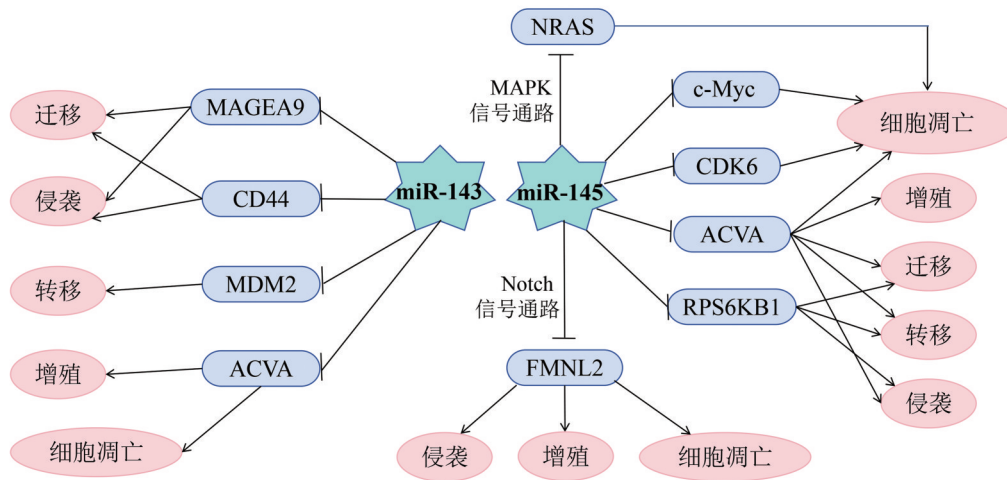


图 3 miR-143、miR-145对下游靶基因的调控

Fig 3 Regulation of miR-143 and miR-145 on downstream target genes

2.4 miR-143、miR-145在OSCC中的上游调控

2.4.1 miR-143的上游调控

Wang等^[41]发现circ-PVT1能抑制miR-143-3p的表达,间接上调溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)和MAPK的表达,沉默circPVT1则阻碍了OSCC通过miR-143-3p/SLC7A11轴和miR-143-3p/MAPK轴驱动的进展。马稔秋等^[42]观察到OSCC组织和细胞系中LINC00705高表达,miR-143-3p低表达,且呈负相关,LINC00705可通过下调miR-143-3p增强OSCC细胞的增殖和转移能力。

2.4.2 miR-145的上游调控

Ai等^[43]证实,在OSCC细胞系和肿瘤组织中circ0001461高表达,circ0001461通过抑制miR-145促进细胞增殖、迁移和侵袭,并通过调节miR-145/Toll样受体4(Toll like receptor 4, TLR4)/核因子(nuclear factor, NF)- κ B通路,增强了细胞对肿瘤坏死因子(tumor necrosis factor, TNF) α 诱导的凋亡抗性。Lu等^[44]发现circZNF236通过靶向抑制miR-145-5p间接上调含MBT域1(mbt domain containing 1, MBTD1)表达,促进OSCC发展。Zhou等^[45]观察到circ0058063在OSCC中高表达,并通过上调磷酸肌醇3激酶(phosphoinositide 3 kinase, PI3K)和蛋白激酶B(protein kinase B, AKT)的磷酸化水平促进肿瘤生长,而miR-145-5p的过表达能显著抑制PI3K/AKT通路,进而削弱OSCC的恶性潜能。Arun Kumar等^[46]在lncRNA RoR过表达的未分化肿瘤样本中发现miR-145-5p表达

极低,lncRNA RoR可靶向抑制miR-145-5p,进而减轻其对c-Myc、Krüppel样因子4(Krüppel-like factor 4, KLF4)、POU5类同源框1(POU class 5 homeobox 1, POU5F1)和SRY-Box转录因子2(SRY-box transcription factor 2, SOX2)等靶基因的调控,影响细胞的增殖和侵袭能力。这些研究揭示了以miR-143、miR-145为中心的复杂调控网络,其中circ-RNA和lncRNA通过影响miR-143和miR-145的表达,间接调控OSCC的发展。miR-143、miR-145的上游调控总结见图4。

3 miR-143/145在OSCC中的应用展望

miRNA在肿瘤发展中的重要性日益突显。在临床和临床前研究中,miRNA表现出广泛的应用前景,包括但不限于作为肿瘤生物标志物、药物靶点和治疗工具。通过检测肿瘤组织或血液循环中的miRNA差异表达,可以为肿瘤的诊断、预后评估和治疗敏感性提供重要信息^[47-50]。例如,在OSCC患者的血浆中,包括miR-146a和miR-187在内的16种miRNA显著上调,10种miRNA显著下调,这些差异表达的miRNA有助于OSCC的早期筛查^[51]。

此外,检测OSCC患者唾液中的miRNA表达谱也有助于早期诊断和疾病监测,如miR-21和miR-31的上调联合miR-200a和miR-125a的下调^[52]。miR-149-3p、miR-182-5p和miR-105等差异表达的miRNAs在OSCC的疾病进展和预后中也具有预测

作用^[53-55]。一些miRNA在推动OSCC进程中起到关键作用,为药物开发和治疗靶点选择提供了新思

路,如miR-31和miR-34a-3p^[56-57]。

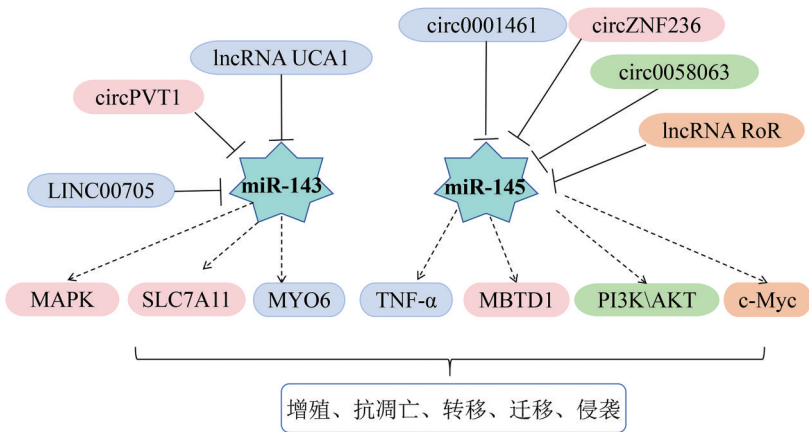


图 4 miR-143、miR-145 的上游调控

Fig 4 The upstream regulation of miR-143 and miR-145

miR-143和miR-145作为新兴的关键分子,通过与上游ceRNA分子相互作用和调控下游靶基因参与OSCC演进过程。miR-143和miR-145在OSCC及循环血液中的差异表达,显示它们作为生物标志物在辅助临床筛查、诊断和预后评估中的潜力。借助液体活检技术,这些miRNA有助于提高疾病的早期检出率,构建个体化治疗方案,并准确评估治疗效果和预后^[58]。此外,CRISPR/Cas13技术为miRNA的研究和治疗带来了新的突破。这种技术不仅能精确编辑特定miRNA,还能在细胞层面调控其靶基因的表达,提供了靶向调控OSCC患者体内miR-143和miR-145表达水平的新途径,为个体化治疗开辟了新路径。尽管如此,目前尚不清楚miR-143和miR-145在调控靶基因时是否作为基因簇发挥协同作用,或是各自独立地发挥作用。未来的研究需要揭示这2种miRNA的具体作用机制及其在OSCC中的相互作用,以更好地利用其潜力,为OSCC的治疗和管理提供新的策略。

4 小结

miR-143和miR-145作为关键的肿瘤抑制因子,在OSCC的发生发展中扮演重要角色。二者通过靶向调控下游多个致癌信号通路的关键分子抑制OSCC的恶性生物学行为。此外, circRNA和lncRNA作为上游调控分子可靶向抑制miR-143和miR-145,间接激活促癌通路,进一步推动OSCC演进。未来研究需结合多组学技术、类器官模型及临床队列验证,系统阐明以miR-143和miR-145为中心的上

下游调控机制,以全面理解其在肿瘤发生中的作用,并推动其从基础研究向临床转化,为OSCC的精准治疗开辟新途径。

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