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· 基础研究 ·

miR-135b-5p在口腔鳞状细胞癌中的表达及相关生物信息学分析

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【摘要】 目的 探索 miR-135b-5p 在口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)及癌旁组织中的表达及其临床意义, 预测 miR-135b-5p 靶基因并进行相关生物信息学分析。**方法** 通过肿瘤与癌症基因组图谱(the Cancer Genome Atlas, TCGA)、基因表达数据库(Gene Expression Omnibus, GEO)数据库分析 miR-135b-5p 在 OSCC 组织和癌旁组织中的表达并分析其临床意义; 临床收集新鲜组织标本, 采用实时荧光定量 PCR 验证不同组织中 miR-135b-5p 的表达情况。采用生物信息学方法预测 miR-135b-5p 的靶基因并进行通路富集分析。构建蛋白互作网络筛选关键靶基因。**结果** OSCC 组织中 miR-135b-5p 表达量较癌旁组织上调, 差异有统计学意义($P < 0.001$); miR-135b-5p 表达量对 OSCC 组织具有良好的诊断效能($AUC = 0.960$, $P < 0.001$); OSCC 组织中 miR-135b-5p 表达水平与组织病理分级相关($P = 0.011$); 生信分析结果显示, miR-135b-5p 的靶基因富集在与肿瘤相关的钙离子、cGMP-PKG、cAMP 信号通路中; 筛选得到 10 个关键靶基因: DLG2、ANK3、ERBB4、SCN2B、NBEA、GABRB2、ATP2B2、SNTA1、CACNA1D、SPTBN4。**结论** miR-135b-5p 可作为一种促癌基因参与 OSCC 的发生发展, 并具有成为 OSCC 诊断标志物及治疗靶点的潜在应用价值。

【关键词】 口腔鳞状细胞癌; 微小RNA; miR-135b-5p; 生物信息学; 癌症基因组图谱; 基因表达数据库; 靶基因; 钙离子信号通路; 肿瘤分子标志物

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Expression and relevant bioinformatics analysis of miR-135b-5p in oral squamous cell carcinoma ZHAO Ge, LI Changxue, GUO Chao, ZHU Hui. Department of Stomatology, the First Affiliated Hospital, School of Medicine, Shihezi University, Shihezi 832000, China

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【Abstract】 Objective To observe the clinical significance of miR-135b-5p in oral squamous cell carcinoma (OSCC) tissues and to conduct a bioinformatics analysis of its predicted target genes. **Methods** The expression levels of miR-135b-5p in OSCC tissues and adjacent normal tissues were compared using data from TCGA and GEO databases, and the correlations of miR-135b-5p expression level with clinicopathologic characteristics were analyzed. Fresh tissues were collected in the clinic, and the expression of miR-135b-5p was verified by quantitative real-time PCR. The target genes with enriched pathways were analyzed by using bioinformatics methods. A protein-protein interaction network was constructed to screen hub genes. **Results** The expression levels of miR-135b-5p were significantly upregulated in OSCC tissues compared to adjacent normal tissues ($P < 0.001$) and had a good diagnostic capability ($AUC = 0.960$, $P < 0.001$). The expression level of miR-135b-5p was positively correlated with histopathological grading ($P = 0.011$). Enrichment analyses revealed that the target genes of miR-135b-5p were significantly associated with tumor-related signal-

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ing pathways, such as the calcium signaling pathway, the cGMP-PKG signaling pathway and the cAMP signaling pathway. Ten core target genes were obtained by screening: DLG2, ANK3, ERBB4, SCN2B, NBEA, GABRB2, ATP2B2, SN-TA1, CACNA1D, and SPTBN4. **Conclusion** miR-135b-5p may act as an oncogene miRNA in OSCC and has the potential value of acting as a diagnostic biomarker and therapeutic target for OSCC.

【Key words】 oral squamous cell carcinoma; microRNA; miR-135b-5p; bioinformatics analysis; the Cancer Genome Atlas; Gene Expression Omnibus; target gene; calcium signaling pathway; tumor molecular marker

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口腔癌为全球第九大恶性肿瘤,约90%以上的口腔癌是口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC),虽然近年来治疗 OSCC 的手术和放疗技术有了一定进步,但5年生存率仍仅为50%左右^[1]。随着分子生物学的发展,越来越多的研究显示微小RNA(microRNA, miRNA)在肿瘤细胞的生长、分化、增殖和凋亡等过程中发挥了重要的作用^[2]。miR-135b-5p在胰腺癌^[3]、胃癌^[4]、结直肠癌^[5]等恶性肿瘤中异常高表达,但miR-135b-5p在OSCC中的表达情况尚不明确。本研究通过对公开发表的转录组测序数据、基因芯片数据进行分析,辅以新鲜组织样本实验验证,探讨miR-135b-5p在OSCC患者中的表达水平及其与临床特征的关系。同时采用生物信息学方法预测miR-135b-5p的靶基因并进行通路富集分析。

1 资料和方法

1.1 研究资料

肿瘤与癌症基因组图谱(the Cancer Genome Atlas, TCGA)中下载与OSCC相关的miR-135b-5p表达数据(247例癌组织,17例癌旁组织)及其完整的临床资料(222例);与OSCC相关的mRNA表达信息(240例癌组织,17例癌旁组织)。基因表达数据库(Gene Expression Omnibus, GEO)下载OSCC相关基因表达谱数据GSE45238(40例癌与癌旁配对组织)。收集石河子大学医学院第一附属医院2017年1月至2020年6月手术切除的30例口腔鳞癌组织和癌旁组织(距癌组织边缘 ≥ 2 cm)。所有OSCC患者手术前均未接受放疗或化疗。所有手术取材标本离体后立即放置在液氮中,后储存在-80℃冰箱中。本研究由石河子大学医学院第一附属医院伦理委员会批准(文件编号:AF/SC-08/01.0),本研究

收集的标本已取得患者的书面知情同意。

1.2 研究方法

1.2.1 公共数据库中miR-135b-5p表达分析 TCGA、GEO官网下载OSCC组织及癌旁组织中miR-135b-5p原始表达数据,标准化处理后行差异分析。将miR-135b-5p表达信息与临床信息合并,用于后续临床相关性分析。使用R语言edgeR包筛选出TCGA下载的mRNA表达谱中的差异表达的mRNA。

1.2.2 新鲜组织中miR-135b-5p表达分析 依据Biospin miRNA Extraction Kit试剂盒说明完成组织中miRNA提取,测量OD260/280值在1.8~2.0之间。使用miRNA ALL-IN-One cDNA Synthesis Kit将总miRNA反转录成cDNA。以U6为内参(表1),使用EvaGreen miRNA qPCR Master Mix-Low ROX试剂盒进行实时荧光定量聚合酶链式反应(quantitative Real-Time PCR, qRT-PCR)。扩增反应条件如下:预变性95℃ 10 min,1个循环;变性95℃ 10 s,退火58℃ 30 s,延伸72℃ 30 s,40个循环。所有反应均设置3个复孔以减少加样等造成的误差影响实验结果。扩增反应结束后分析溶解曲线,判断扩增产物是否存在非特异性扩增。分析扩增曲线,采用 $2^{-\Delta\Delta Ct}$ 计算miR-135b-5p在OSCC组织中的相对表达量。

表1 miR-135b-5p的实时荧光定量PCR扩增引物序列

Table 1 Primer sequence of miR-135b-5p qRT-PCR amplification

Gene	Primer	Primer Sequence
U6	Forward	CTCGCTTCGGCAGCACA
U6	Reverse	AACGCTTCACGAATTTGCGT
miR-135b-5p	Forward	TATGGCTTTTCATTCTATGTGA
miR-135b-5p	Reverse	TGGTGTCTGGAGTCTG

1.2.3 miR-135b-5p靶基因预测及功能富集分析 从 miRTarBase、targetScan 和 miRDB 三个数据库预测 miR-135b-5p 的靶基因,选取至少 2 个数据库中预测到的靶基因与 TCGA 数据库下载分析的差异 mRNA 取交集。通过 R 语言对这些交叉基因进行京都基因与基因组百科全书(kyoto encyclopedia of genes and genomes, KEGG)通路富集分析。

1.2.4 miR-135b-5p 关键靶基因筛选 通过 STRING 数据库绘制蛋白互作网络(protein-protein interaction network, PPI)用于揭示靶基因之间的关系,置信度参数为 0.400。使用 Cytoscape3.6.1 及其插件 cytoHubba 筛选出前 10 个关键靶基因。

1.3 统计学方法

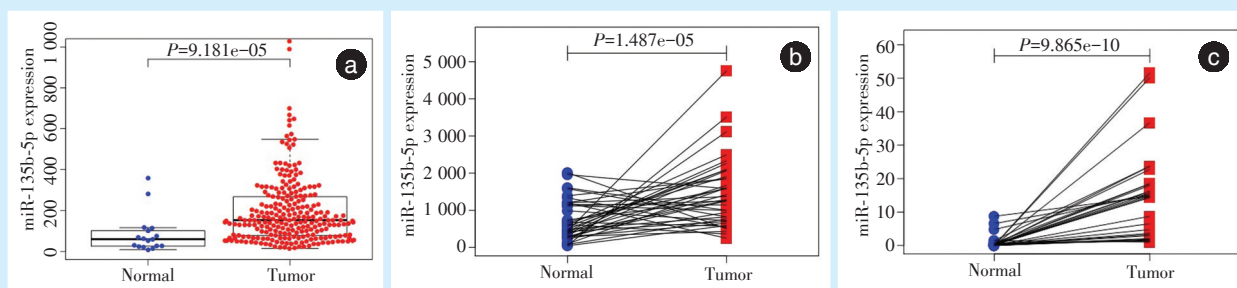
使用 R 语言 3.6.3 及其附属包进行统计分析并绘图。两组间差异采用 Wilcoxon 检验。卡方检验

分析 miR-135b-5p 表达情况与 OSCC 患者临床病理特征关系。通过受试者工作特征曲线(receiver operator characteristic curve, ROC)分析评价 miR-135b-5p 表达对于 OSCC 患者诊断的准确性。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 miR-135b-5p 在 OSCC 组织及癌旁组织中的表达差异

TCGA、GEO 官网下载 OSCC 组织原始表达数据,以及本研究新鲜组织中 miR-135b-5p 的 qRT-PCR 结果的分析显示,OSCC 组织中 miR-135b-5p 表达量高于癌旁组织,差异具有统计学意义($P < 0.001$)。见图 1。



Data were obtained from (a) TCGA database, (b) GEO database and (c) qRT-PCR result of fresh tissues. miR-135b-5p was highly expressed in oral squamous cell carcinoma compared with paracancerous normal tissues

Figure 1 miR-135b-5p is frequently increased in oral squamous cell carcinoma cancer tissues

图1 miR-135b-5p在口腔鳞状细胞癌组织中高表达

2.2 miR-135b-5p表达水平与临床病理关系

TCGA 中下载与 OSCC 相关的 miR-135b-5p 表达数据及其完整的临床资料(222 例), χ^2 检验表明 miR-135b-5p 表达水平与肿瘤组织病理分级相关($P = 0.011$),但与年龄、性别、临床分期、淋巴结转移情况不相关($P > 0.05$)(表 2)。miR-135b-5p 对 OSCC 具有较好的辅助诊断效能($AUC = 0.960$, $P < 0.001$)(图 2)。

2.3 miR-135b-5p 靶基因预测及功能分析

3 个软件预测的靶基因数分别为 804、83、537, 取任意两软件预测结果的交集(共 503 个)(图 3)。为了进一步提高生物信息学分析的可靠性,与 TCGA 下载分析出的差异 mRNA 取交集,最终筛选出与 miR-135b-5p 表达相反的靶基因共 60 个。对 60 个靶基因进行 KEGG 通路富集研究,富集集

中在与肿瘤相关的钙离子信号通路、cGMP-PKG 信号通路和 cAMP 信号通路中(表 3)($P < 0.05$)。

2.4 miR-135b-5p 关键靶基因筛选

上述得到的 60 个预测靶基因中,共有 35 个被过滤到靶基因 PPI 网络中,筛选得到 10 个关键靶基因(图 4),分别为大同源物 2(discs-large homolog 2, DLG2)、锚蛋白重复序列 3(ankyrin repeat 3, ANK3)、Erb-B2 受体酪氨酸激酶 4(Erb-B2 receptor tyrosine kinase 4, ERBB4)、电压门控性钠通道二型 beta 亚单位(sodium channel voltage-gated type II beta, SCN2B)、蛋白激酶锚定蛋白(neurobeachin, NBEA)、 γ -氨基丁酸 $\beta 2$ 亚基(γ -aminobutyric acid neurotransmitter receptor $\beta 2$ subunit gene, GABRB2)、质膜钙 ATP 酶异构体 2(plasma membrane calcium ATPase 2, ATP2B2)、 α -互养蛋白(α -syntro-

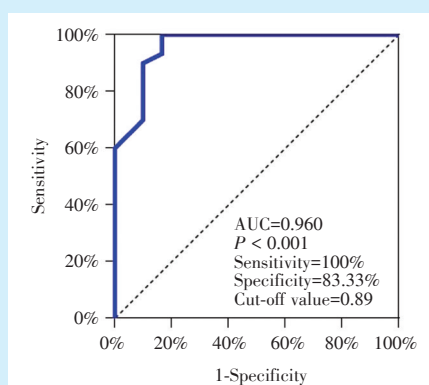
表2 miR-135b-5p表达与临床病理相关性
Table 2 miR-135b-5p expression associated with clinical pathological characteristics

Clinicopathological factor	miR-135b-5p expression		Case	χ^2	P
	High	Low			
Age/year					
≤ 60	55	56	111	0.018	0.893
> 60	56	55	111		
Gender					
Male	74	73	147	0.020	0.887
Female	37	38	75		
Clinical stages					
I+II	28	25	53	0.223	0.637
III+IV	83	86	169		
Histopathological grading					
G1+G2	82	97	179	6.490	0.011
G3	29	14	43		
Lymph node status					
N0	51	49	100	0.073	0.787
N1+N2+N3	60	62	122		

phin, SNTA1)、钙电压门控通道亚单位 $\alpha 1D$ (calcium voltage-gated channel subunit $\alpha 1D$, CACNA1D)、血影蛋白 β 非红细胞4(spectrin beta non-erythrocytic 4, SPTBN4)。

3 讨论

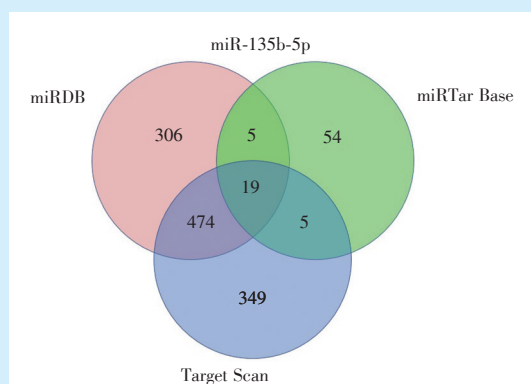
OSCC的发生发展是一个多阶段、多步骤、多基因、多通路调控的复杂过程^[6]。miRNA表达异常在肿瘤的发生、发展中发挥着重要作用,深入研究miRNA与肿瘤的相关性将有望为肿瘤的诊断及靶向治疗提供新的思路。miR-135b位于1号染色体上,有miR-135b-5p和miR-135b-3p两种剪切成熟体^[7]。miR-135b作为一种促癌因子,在多种肿瘤中均有着重要的作用,控制着癌细胞的生物学行为并影响耐药,如:高表达的miR-135b-5p可通过靶向NR3C2促进胰腺癌细胞的迁移、侵袭和上皮间质转化^[3],可抑制胃癌细胞凋亡并诱导顺铂耐



The area under the receiver operating characteristic curve was 0.960. When the cut-off value was 0.89, the sensitivity was 100%, and the specificity was 83.33%. Thus, this marker has high diagnostic efficacy for oral squamous cell carcinoma, AUC: area under curve

Figure 2 Receiver operating characteristic curve of miR-135b-5p in the diagnosis of oral squamous cell carcinoma

图2 miR-135b-5p诊断口腔鳞状细胞癌的受试者工作曲线



The target genes of miR-135b-5p were predicted by the miRDB, miRTAR Base and Target Scan databases, and 503 target genes were obtained by intersecting each pair of databases

Figure 3 Venn diagram of predicted target genes of miR-135b-5p

图3 miR-135b-5p的预测靶基因数目韦恩图

药^[4];抑制miR-135b的表达能够抑制结大肠癌细胞的增殖,提高患者对奥沙利铂的敏感性^[8],降低鼻咽癌细胞的增殖、迁移和侵袭能力^[9]。

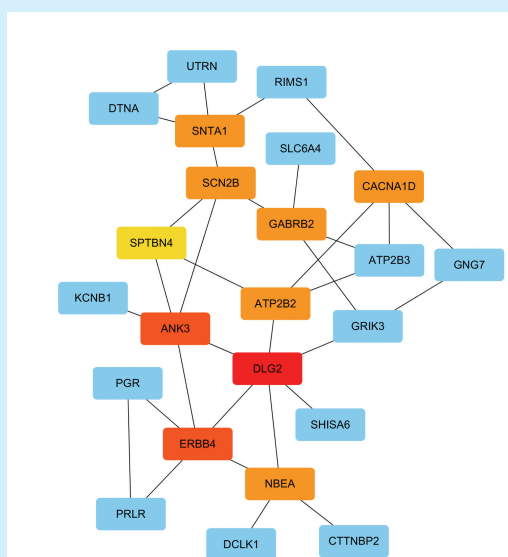
目前miR-135b-5p在OSCC中的表达情况仍存在争议。有研究表明,微阵列实验结果显示miR-135b在OSCC中呈低表达;而另有研究证明miR-

表3 miR-135b-5p靶基因KEGG信号通路显著性富集分析结果

Table 3 Significantly enriched KEGG pathways of target genes of miR-135b-5p

ID	Description	P	Target gene ID
hsa05032	Morphine addiction	< 0.001	PDE1C/GNG7/PDE3B/GABRB2/PDE7B
hsa04020	Calcium signaling pathway	< 0.001	ATP2B3/PDE1C/ERBB4/CACNA1D/ATP2B2
hsa04726	Serotonergic synapse	< 0.001	GNG7/SLC6A4/GABRB2/CACNA1D
hsa04723	Retrograde endocannabinoid signaling	< 0.001	GNG7/RIMS1/GABRB2/CACNA1D
hsa04924	Renin secretion	0.001	PDE1C/PDE3B/CACNA1D
hsa04022	cGMP-PKG signaling pathway	0.001	ATP2B3/PDE3B/CACNA1D/ATP2B2
hsa04727	GABAergic synapse	0.002	GNG7/GABRB2/CACNA1D
hsa04925	Aldosterone synthesis and secretion	0.003	ATP2B3/CACNA1D/ATP2B2
hsa04024	cAMP signaling pathway	0.004	ATP2B3/PDE3B/CACNA1D/ATP2B2
hsa04724	Glutamatergic synapse	0.005	GRIK3/GNG7/CACNA1D

KEGG: Kyoto Encyclopedia of Genes and Genomes; PDE1C: phosphodiesterase 1C; GNG7: guanine nucleotide-binding protein γ 7; PDE3B: phosphodiesterase 3B; GABRB2: γ -aminobutyric acid neurotransmitter receptor β 2 subunit gene; PDE7B: phosphodiesterase 7B; ATP2B3: plasma membrane calcium ATPase 3; ERBB4: erb-B2 receptor tyrosine kinase 4; CACNA1D: calcium voltage-gated channel subunit alpha1 D; ATP2B2: plasma membrane calcium ATPase 2; SLC6A4: solute carrier family 6 member 4; RIMS1: rab-interacting molecules 1



Ten hub genes were screened by Cytoscape software: the darker the color, the more important the function in the interaction. DLG2: discs-large homolog 2; ANK3: ankyrin repeat 3; ERBB4: erb-B2 receptor tyrosine kinase 4; SCN2B: sodium channel voltage-gated type II beta; NBEA: neurobeachin; GABRB2: γ -aminobutyric acid neurotransmitter receptor β 2 subunit gene; ATP2B2: plasma membrane calcium ATPase 2; SNTA1: α -syntrophin; CACNA1D: calcium voltage-gated channel subunit alpha1 D; SPTBN4: spectrin beta non-erythrocytic 4; UTRN: background Utrophin; DTNA: dystrobrevin- α ; RIMS1: rab-interacting molecules 1; SLC6A4: solute carrier family 6 member 4; ATP2B3: plasma membrane calcium ATPase 3; GNG7: guanine nucleotide-binding protein γ -7; KCN1: voltage-gated potassium channel sub-family B member 1; GRIK3: glutamate ionotropic receptor Kainate type subunit 3; PGR: epithelial progesterone receptor; SHISA6: shisa family member 6; PRLR: prolactin receptor; DCLK1: doublecortin-like kinase1; CTTNBP2: cortactin binding protein 2

Figure 4 Hub genes of protein-protein interaction network

图4 蛋白互作网络的关键靶基因

135b-5p 在 OSCC 中呈高表达^[10]。为了进一步明确 miR-135b-5p 在 OSCC 中的表达情况,本研究首先基于 TCGA、GEO 数据库大样本优势分析了 OSCC 组织中 miR-135b-5p 的表达情况,后辅以新鲜组织进行体外实验验证。实验结果均表明 miR-135b-5p 在 OSCC 组织中高表达,差异有统计学意义;且 miR-135b-5p 表达量对于 OSCC 具有良好的诊断效能。此外 OSCC 组织中 miR-135b-5p 表达与病理分级相关,低分化程度患者组织中 miR-135b-5p 表达量高于高中分化患者,差异具有统计学意义。Kademan 等^[11]发现每升高一个组织学等级,患者生存率降低 44%,组织学等级是预测生存率的独立因素。

研究表明低分化的细胞由于缺乏凝聚力,具有单细胞侵袭模式,随着细胞分化程度的降低,淋巴结转移的机会会增加^[12]。因此笔者推测,作为诊断标志物的 miR-135b-5p 的高表达可能预示着不良预后。

miRNAs 是转录后水平调控基因表达的关键分子。KEGG 富集分析结果显示,miR-135b-5p 的预测靶基因集中富集在与肿瘤密切相关的 3 个通路中:钙离子、cGMP-PKG、cAMP 信号通路。这些通路都是与肿瘤增殖、分化、凋亡、侵袭、转移等生物学行为密切相关的信号通路^[13-15]。这与前述的关于 miR-135b-5p 影响多种肿瘤细胞不良生物学行

为和耐药的实验研究结论相一致^[3-4]。构建蛋白互作网络,筛选出10个重要的中枢蛋白:DLG2、ANK3、ERBB4、SCN2B、NBEA、GABRB2、ATP2B2、SNTA1、CACNA1D、SPTBN4。其中CACNA1D和ATP2B2均参与了上述3个癌症相关通路。乳腺癌中miR-135b低表达,ATP2B2高表达,ATP2B2减少了肿瘤细胞内钙离子进而抑制了细胞凋亡^[16]。这与笔者预测的ATP2B2参与调控钙离子通路的结果一致。CACNA1D在肾癌和肺癌中均低表达^[17],前列腺癌中低表达的CANCA1D提示肿瘤的恶性程度更高,侵袭性更强^[18],有望成为癌症治疗的新靶点。本实验通过生物信息学分析,得到的miR-135b-5p的关键靶基因及癌症相关的靶向调控的信号通路,为后续机制研究提供方向。

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