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·综述·

microRNA 与口腔鳞状细胞癌的研究新进展

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[摘 要] microRNA即miRNA，又被称为微小RNA，是一组由18~24个核苷酸长度组成的内源性非编码单链RNA，研究发现miRNA在包括口腔鳞状细胞癌在内的恶性肿瘤的发生发展中起重要的调控作用。以miRNA为靶标的靶向治疗受到人们的关注，针对miRNA的研究或许能为口腔鳞状细胞癌的治疗找到新的策略。

[关键词] microRNA；口腔鳞状细胞癌；诊断靶向治疗

Recent advances in the research of microRNA in oral squamous cell carcinoma

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Abstract MicroRNA or miRNA, is a group of which endogenous non-single stranded RNA composed of 18–24 nucleotides in length. miRNA was found in malignant tumors plays an important role in the development of oral squamous cell carcinoma. MiRNAs have been focused on targeted therapy. Studying on miRNA may find a new strategy for the treatment of oral squamous cell carcinoma. The roles of miRNA in the new research progress of OSCC development and the effect of diagnosis and treatment are reviewed.

Keywords microRNA; oral squamous cell carcinoma; diagnosis targeted therapy

口腔癌是世界范围内第六大常见癌症，其中口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)所占比例超过90%[1]，尽管辅助性放射治疗和化学治疗取得了显著进展，但OSCC患者的5年生存率仍然无明显改善[2]，晚期诊断、淋巴结转移[3]及复发是OSCC患者不良预后与低生存率的主要原因。因此，迫切需要可靠的分子标志物为OSCC患者提供更早、更明确的诊断及最精准的靶向治疗。近年来，越来越多的研究[4-5]证实肿瘤抑制基因与癌基因在编码蛋白质中的变化是肿瘤发生发展的主要动力之一；研究[6]发现miRNA与OSCC的发生发展密切相关，miRNA可以与靶mRNA的3'-UTR结合，

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单个miRNA可以调节数百个靶mRNA与蛋白质的表达和功能，并调控对癌症发展至关重要的生物学过程，如细胞增殖、侵袭迁移、信号转导等。

1 OSCC中miRNA的异常表达谱

Wong等[7]在舌鳞癌和相邻正常上皮组织中进行了关于舌鳞癌中miRNA表达谱的分析，研究了舌鳞癌细胞中156个成熟miRNA的表达情况，发现与正常的上皮细胞相比，舌鳞癌细胞中miR-133a与miR-133b显著下调。另一项研究[8]使用微阵列分析10例舌鳞癌中miRNA的表达，在舌鳞癌与正常舌组织中观察到显著差异表达的71个miRNA，在4例早期舌鳞癌组织中鉴定出10个上调miRNA与15个下调miRNA，而在另外6例晚期舌鳞癌组织中鉴定出26个上调miRNA与2个下调miRNA。最近的miRNA测序分析OSCC组织中45个miRNA上调，17个miRNA下调[9]。随着对miRNA不断深入的研究，在OSCC，TCA8113和Cal27细胞系中发现了更多异常表达的miRNA(表1)。

表1 OSCC中miRNA异常表达谱

Table 1 Abnormal expression profile of miRNA in OSCC

细胞系	上调	下调
OSCC	Let-7a，miR-16，miR-203，miR-21，miR-27a，miR-27b，miR-17-5p[7]，miR-195[10]，miR-221[11]	miR-26b，miR-148a，miR-320，miR-451，miR-513，miR-519b，miR-133a-3p[12]，miR-99a[13]
Tca8113	Let-7c，Let-7d，Let-7e，Let-7g，miR-20b，miR-23a，miR-30d，miR-181d，miR-188，miR-214，miR-373，miR-432，miR-498，miR-518c，miR-584，miR-608，miR-628[14]	miR-342，miR-375[15]，miR-21-5p[16]
Cal27	Let-7e，miR-193a-5p，miR-30c-1，miR-342-3p，miR-342-5p，miR-452，miR-486-3p，miR-518b，miR-628-3p，miR-663，miR-675，miR-877[17]，miR-518c-5p[18]	Let-7b，let-7e，let-7f，let-7i，miR-15b，miR-20a，miR-21，miR-27b，miR-886-3p，miR-93，miR-98[17]，miR-137[19]

2 miRNA与OSCC

2.1 miRNA与OSCC的发生

多项研究[20-21]显示许多miRNA在OSCC中被上调或者下调并且起癌基因的作用。据报道[22]，与其正常组织相比，miR-184在舌鳞状细胞癌(tongue squamous cell carcinoma，TSCC)中表达上调，miR-184抑制剂通过靶向c-Myc降低OSCC细胞系CAL27，HN21B及HN96的细胞增殖率与诱导细胞凋亡。此外，在TSCC肿瘤样本和细胞系中过表达的miR-24直接靶向RNA结合蛋白DND1并下调其表达，进而抑制细胞周期蛋白的表达依赖性激酶抑制剂1B(cyclin-dependent kinase inhibitor，CDKN1B)，最终导致TSCC细胞增殖增加和凋亡减少[23]。miR-21已被证明是被过度表达并调节OSCC中的生物学功能[24]。与正常口腔黏膜相比，口腔癌前病变(口腔白斑病)中也观察到miR-21的过度表达[25]，表明miR-21的改变可能是OSCC早期进展中已经发生，许多体外和体内实验[26-27]通过促进细胞增殖，侵袭，抗细胞凋亡和化学耐药性证明了miR-21在OSCC中的致癌作用。除OSCC细胞的功能作用外，越来越多的证据[24]表明miR-21可能在诱导癌相关成纤维细胞(carcinoma-associated fibroblasts，CAFs)及调控其活性中非常重要，且显示miR-21主要位于OSCC基质中并与α-SMA阳性CAFs共定位。研究[28]发现在OSCC样本与UPCI-SCC-116S细胞系中miR-377下调可以通过靶向HDAC9促进OSCC细胞的生长和迁徙。以上研究均表明miRNA与肿瘤的发生关系密切。

2.2 miRNA与OSCC进展

2.2.1 miRNA与肿瘤细胞增殖

肿瘤细胞的增殖与迁移是肿瘤发生发展的基础，直接参与肿瘤细胞增殖主要包括细胞周期相关蛋白(如细胞周期依赖性蛋白CDK)的变化与生长因子[如血小板衍生生长因子(platelet-derived growth factor，PDGF)]及其受体2个方面，近年来研究[29]发现miRNA参与促进了多种肿瘤细胞的增殖迁移而加快肿瘤进展。上皮细胞分泌产生的PDGF家族可以通过自分泌和旁分泌途径促进肿瘤细胞增殖分化，研究[30]发现PDGF-BB通过miR-21介导PDCD4的下调刺激细胞增殖，促进肿瘤进展。细胞周期依赖性蛋白主要通过调控细胞周期，加速肿瘤细胞增殖分化，加速肿瘤发生发展，miR-148a通过调节CDKN1B参与多发性骨髓瘤细胞RPMI8226的生长与增殖[31]。上述研究均表明

miRNA参与调控肿瘤细胞的增殖迁徙而促进肿瘤进展。

2.2.2 miRNA与肿瘤血管生成

肿瘤血管生成是一个连续复杂的过程，为肿瘤的生长提供营养代谢基础，同时因其内皮不完整与高通透性也为肿瘤转移提供了有利条件。OSCC为侵袭性肿瘤，表现出缺氧和生长因子不足的特点，导致肿瘤中心发生大面积坏死。有研究[32]表明缺氧介导了数百种基因表达变化，其通过缺氧诱导因子1α(hypoxia-inducible factor 1α，HIF1-α)转录因子的活性影响肿瘤发生的许多方面，缺氧的肿瘤微环境可促进血管生成因子和肿瘤血管生成，内皮细胞是一类重要的促血管生成因子，如VEGF。miRNA可以通过调控内皮细胞的生物学行为而影响血管生成[33]，最近的研究[34]也证实miRNA的失调与肿瘤的发生有关，特别是肿瘤血管生成。miR-296是已知能够促进血管发生的研究最多的miRNA之一[35-36]。下调的miR-126通过靶向VEGF-A增加肿瘤血管密度，加快肿瘤进展[37]。以上研究均表明miRNA可以通过促进肿瘤血管生成从而促进肿瘤的进展。

2.3 miRNA与OSCC的侵袭转移

2.3.1 miRNA与OSCC上皮间质转化

上皮间质转化(epithelial-mesenchymal transition，EMT)是上皮细胞向间质转化的过程，研究[38]发现EMT是肿瘤细胞定植、侵袭及转移的关键因素，因此，EMT与肿瘤之间的关系是癌症研究的重点。许多研究[39-42]结果指出miRNA有调控OSCC细胞EMT与EMT相关恶性表型的作用，主要包括以下3个方面：1)细胞内细胞蛋白水平变化。E-钙黏蛋白[39]，β-连环蛋白及细胞角蛋白等上皮标志物蛋白的表达降低；它还着重于间充质标志蛋白如N-钙黏蛋白与波形蛋白的表达增加[40]。2)细胞表型和生物行为改变。使上皮细胞失去其极性并与基底膜连接，然后转化为具有较高迁移和侵袭倾向，抗细胞凋亡特征和细胞外基质产生的间充质表型，当EMT发生时，往往会增加细胞的迁移能力并引起恶性肿瘤的侵袭。在OSCC组织中，miR-143/miR-145簇的下调可以激活活化素A高表达[41]，从而促进肿瘤细胞的增殖和迁移能力。3)表观遗传学。OSCC表观遗传学研究[42]发现EMT的发生与基因组的表观遗传重编程相关，包括DNA甲基化和组蛋白的翻译后修饰，这些变化可以促进基质基因的表达或抑制与上皮表型有关的基因的表达。以上研究均表明miRNA可以通过促进EMT而调控OSCC细胞恶性表型。

2.3.2 miRNA与OSCC淋巴结转移

淋巴结转移是OSCC转移的主要途径，研究[43]表明miRNA可以刺激肿瘤淋巴管新生为肿瘤的转移提供通道。乳腺肿瘤标本qRT-PCR实验发现：与正常组织相比，miR-218在乳腺肿瘤组织中低表达，并且与淋巴结转移和较差预后相关[44]。动物实验研究[45]发现下调的miR-204可以刺激淋巴管新生导致OSCC淋巴结转移。Tu等[46]通过激光捕获显微切割分离纯化正常口腔上皮和OSCC组织，发现OSCC组织中miR-372和miR-373过表达，并且与淋巴管侵袭、淋巴结转移及低生存率密切相关。原位异种移植瘤模型研究[47]发现：miR-21过表达导致原发肿瘤体积和重量增加，并且增加了淋巴结转移率。这些研究证明miRNA在OSCC淋巴结转移中发挥了重要作用。

2.3.3 miRNA与OSCC侵袭转移相关信号通路

miRNA还可通过调控相关信号通路促进OSCC的侵袭转移。参与调控OSCC侵袭转移的主要信号通路如下：1)Jensen等[48]通过RNA测序和miRNA-qPCR阵列分析发现miR-200可以通过激活TGF-β/SMAD通路促进EMT的发生，最终导致OSCC不良预后；2)miR-182的过表达可以抑制RASA1和SPRED1而激活Ras/MEK/ERK通路，促进OSCC肿瘤细胞的增殖和侵袭能力；3)miR-92b可以通过调节NLK的表达激活NF-κB信号通路而促进肿瘤的发生[49]；4)体内和体外实验研究[50]证明miR-124可以通过靶向抑制JAG1的翻译和表达而激活Notch信号通路，促进肿瘤细胞的增殖、侵袭及迁移；5)miR-126a可以通过抑制PTEN/AKT信号通路促进卵巢EMT和转移[51]。

3 miRNA与OSCC的诊断与治疗

早期诊断与治疗是OSCC良好预后的关键前提。在不同肿瘤类型中观察到miRNAs的异常表达，这使得它们可能成为诊断与预后标志物及潜在的治疗靶点。现已经发现某些miRNA的表达情况与临床分期、淋巴结转移及OSCC患者预后相关，表明这些miRNA可以作为OSCC的预后预测因子。TSCC中miR-21的较高表达水平与晚期临床分期、差异程度差及淋巴结转移相关[8]。研究[52]发现血浆miR-200b-3p在OSCC中显著上调，在WHO分级中的II和III级中较高，并且在手术后miR-200b-3p水平明显下降，因此血浆miR-200b-3p水平可能是OSCC潜在的诊断生物标志物。miRNA

在OSCC靶向治疗中已经取得初步进展，有研究[53]表明：miR-126可以通过下调ERK信号通路抑制EGLF7，抑制肿瘤血管生成，降低细胞增殖和诱导细胞凋亡。miR-101在OSCC中明显下调，研究[54]发现miR-101可能通过靶向趋化因子受体7(CXCR7)发挥肿瘤抑制功能，抑制OSCC细胞生长、增殖及迁移，因此miR-101很有可能成为OSCC治疗的靶标。近年来还发现了很多OSCC靶向治疗的新靶点，如miR-21[55]，miR-221[11]，miR-155[56]等。这说明miRNA为OSCC的早期诊断与靶向治疗提供了一种新的方法。

4 结语

miRNA与OSCC的多种生物学行为关系密切，但miRNA是如何调控肿瘤细胞增殖侵袭及肿瘤浸润转移的具体分子机制与信号通路尚未完全明确，未来研究者们可以进一步探究miRNA参与调控OSCC发生发展及其侵袭转移的具体分子机制。以miRNA为靶标的靶向治疗有了初步进展，这为OSCC的精准治疗提供了新的策略。

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