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·综述·

环状RNA m6A甲基化修饰在口腔疾病中的研究进展

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【摘要】 N6-甲基腺苷（N6-methyladenosine，m6A）修饰是真核生物最丰富的一种RNA修饰，广泛参与RNA的核输出、剪接、翻译和降解等过程的调控。越来越多的证据表明环状RNA（circular RNA，circRNA）m6A甲基化修饰与代谢、免疫以及良恶性疾病有关。本文对circRNA m6A甲基化修饰在机体生理过程、恶性肿瘤中的作用及口腔疾病中的研究现状作一综述。现有研究显示，m6A甲基化修饰主要通过调节circRNA翻译、促进circRNA的核输出以及促进circRNA降解对circRNA产生影响；circRNA m6A甲基化修饰在免疫、生殖系统、肌细胞发生发育和恶性肿瘤中发挥调控作用；m6A甲基转移酶蛋白3（methyltransferase-like 3，METTL3）通过YTH m6A RNA结合蛋白1（YTH m6A RNA binding protein 1，YTHDF1）介导的m6A修饰促进口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）的发生，METTL14的高表达可有效降低OSCC的增殖、迁移和侵袭；circRNA m6A甲基化修饰在口腔领域的研究较少，仅限于成釉细胞瘤和口腔种植骨吸收方向的初步研究，在口腔重大疾病（如口腔潜在恶性疾病及OSCC）方向有广阔的研究前景。

【关键词】 环状RNA；　非编码RNA；　甲基化修饰；　N6-甲基腺苷；　口腔鳞状细胞癌；　口腔潜在恶性疾病；　口腔；　肿瘤；　生物标志物
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Research progress on m6A-modified circRNA in oral diseases

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【Abstract】 N6-methyladenosine (m6A) modification is the most abundant RNA modification in eukaryotes and is widely involved in the regulation of RNA nuclear export, splicing, translation and degradation. Increasing evidence shows that m6A methylation modification of circular RNA (circRNA) has great potential in metabolism, immunity and benign and malignant diseases. Here, we review the research status of circRNA m6A methylation modification in physiological processes, malignant tumors and oral diseases. It has been shown that m6A methylation can regulate circRNA by regulating circRNA translation, promoting circRNA nuclear output, and promoting circRNA degradation; M6A-modified circRNA plays a regulatory role in immunity, the reproductive system, myogenesis and development, and malignant tumors; and the M6A methyltransferase METTL3 promotes the occurrence of oral squamous cell carcinoma (OSCC) through m6A modification mediated by YTHDF1. The high expression of METTL14 can effectively reduce the proliferation, migration and invasion of OSCC. There is little research on circRNA m6A methylation modification in the oral cavity, which is lim-

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ited to preliminary research in ameloblastoma and oral implant bone absorption. It has broad research prospects in the treatment of major oral diseases (such as potential oral malignant diseases and OSCC).

【Key words】 circular RNA; noncoding RNAs; methylated modification; N6-methyladenosine; oral squamous cell carcinoma; oral potential malignant diseases; oral; tumour; biomarkers

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环状RNA（circular RNA，circRNA）是一种新型非编码RNA，1976年circRNA在植物病毒中被首次发现，描述为“共价闭合的单链环状RNA分子”，起初被认为是RNA异常剪接的副产物[1]。随着RNA测序技术和生物信息学的发展，研究发现circRNA在生物的发生发展过程中发挥了重要作用：miRNA海绵功能、调节可变剪接以及调节基因表达[2]。现已发现circRNA在癌症的发生、发展和耐药性中起着至关重要的作用，且circRNA在外泌体和人体体液中含量丰富，可通过细胞间通讯对肿瘤微环境产生影响[3]。circRNA主要由外显子环化形成，广泛稳定存在于生物体内，在基因表达调控中发挥重要作用，可作为疾病的生物标志物，在临床诊断和治疗方面有广阔的应用前景。N6-甲基腺苷（N6-methyladenosine，m6A）修饰是发生在碱基腺嘌呤（A）第六位N原子上的甲基化，主要发生在RRACH序列中的A上。近年研究发现，m6A甲基化修饰circRNA在人胚胎干细胞中显示出特异性甲基化模式，m6A修饰可促进circRNA降解、核输出，并对circRNA翻译有调控作用[4]。本文就circRNA m6A甲基化修饰在机体生理过程、恶性肿瘤及口腔疾病中的研究现状作一综述。

1　m6A修饰概述

m6A甲基化修饰是一个动态且可逆的过程，这种修饰由3种调节蛋白控制，分别是甲基转移酶、去甲基化酶和阅读蛋白。①甲基转移酶促使RNA m6A甲基化，甲基转移酶样蛋白3/14（methyltransferase-like 3/14，METTL3/14）可形成复合物使RNA m6A甲基化，Wilmstunwell binding蛋白辅助METTL3/14定位并维持体内m6A甲基转移酶的催化活性[5]，此外，RNA结合基序蛋白15/15B（RNA-bindingmotifprotein 15/15B，RBM15/15B）和类病毒m6A甲基转移酶（vir-like m6A methyltransferase associated，VIRMA）在调节METTL3和METTL14活动中发挥重要作用[6]；②去甲基化酶执行RNA去甲基化功能，肥胖相关蛋白（fat mass and obesity-associated protein，FTO）和alkB同源物5（demethylated by human AlkB homolog H5，ALKBH5）一起维持转录组中m6A水平的平衡[7-8]；③阅读蛋白可识别m6A位点并结合甲基化RNA，其中最突出的是含有YTH结构域的RNA结合蛋白，在细胞质中特异性识别m6A修饰的mRNA，能与m6A RRACH片段重叠以介导RNA特异性结合[9]，此外，阅读蛋白还包括异质核核糖核蛋白（eterogeneous nuclear ribonucleoproteins，HNRNP）家族（HNRNPC/HNRNPG/HNRNPL/HNRNPA2B1）[10]、胰岛素样生长因子2结合蛋白家族（insulin-like growth factor 2 mRNA-binding proteins，IGF2BP1/2/3）及PRRC2A。

2　m6A修饰对circRNA的调控作用

2.1　m6A修饰调节circRNA 翻译

Yang等[11]发现m6A基序通过募集YTH m6A RNA结合蛋白1（YTH m6A RNA binding protein 1，YTHDF1）和翻译起始因子eIF4G2/eIF3A启动并诱导circRNA翻译，且数百种的内源性circRNA具有翻译潜力。近期研究表明，m6A修饰可通过YTHDF3和eIF4G2的识别调节circRNA翻译[12]。

2.2　m6A修饰促进circRNA的核输出

Chen等[13]首次发现m6A修饰会促进circRNA的核输出：YTHDC1可与源自NOP2/Sun结构域家族成员2（NOP2/Sun domain family member 2，NSUN2）的circNSUN2结合，促进circNSUN2以m6A依赖性方式从细胞核输出到细胞质。此外有研究发现，Hel25E的同源蛋白UAP56和URH49可介导不同长度的circRNA的出核，然而两者对circRNA长度测量的详细机制仍不清楚[14]。

2.3　m6A修饰促进circRNA降解

由于封闭的环状结构，circRNA不易被水解，往往比其亲本线性RNA更稳定。m6A甲基化修饰的circRNA依赖热反应蛋白-12（heat-responsive protein 12，HRSP12）与YTHDF2结合，通过核糖核

酸内切酶切割选择性降解circRNA[15]。

3　circRNA m6A甲基化修饰在机体生理过程中的作用

3.1　免疫系统

研究表明m6A甲基化修饰可调控免疫反应，circRNA为封闭的环状结构，能逃离末端监控系统。研究发现，机体通过YTHDF2识别m6A以辨认“自身”circRNA，抑制RIG-I激活从而抑制先天免疫[16]。此外，源自NDUFB2的circNDUFB2（hsa_circ_0007518）可触发非小细胞肺癌细胞的免疫防御反应，通过RIG-I识别以激活RIG-I-MAVS信号级联，将免疫细胞募集到肿瘤微环境中[17]。

3.2　生殖系统

在雌性生殖系统中，METTL14介导的m6A甲基化修饰改变了circGFRα1向细胞质的输出，circGFRα1通过充当竞争性内源性RNA促进雌性生殖系干细胞自我更新，吸附miR-449，增强GFRα1表达和激活胶质细胞衍生神经营养因子信号通路[18]。另有研究发现，在雄性生殖细胞中，ALKBH5和METTL3通过调节m6A水平影响circRNA生物合成，circRNA在减数分裂晚期和早期单倍体雄性生殖细胞中积累并发挥作用，持续供应对晚期精子发生和正常精子功能至关重要的蛋白质[19]。

3.3　肌细胞

随着成肌细胞发育分化，eIF4G2和m6A阅读蛋白YTHDF3的mRNA相对表达水平增加，m6A可驱动circRNA翻译，并预测骨骼肌C2C12成肌细胞分化过程中差异表达的circRNA的功能和编码潜力[20]。在高糖处理的血管平滑肌细胞中发现circYTHDC2的稳定受YTHDC2介导的m6A修饰正向调节，而circYTHDC2上调可由血管平滑肌细胞中的高葡萄糖刺激诱导，敲除circYTHDC2可抑制血管平滑肌细胞的增殖和侵袭并阻止细胞周期进程[21]。

4　circRNA m6A甲基化修饰在恶性肿瘤中的作用

此前，m6A甲基化修饰的研究仅局限于mRNA水平，直至2017年Yang等[11]报道了由m6A甲基化驱动的广泛翻译，首次探索了m6A修饰对circRNA的调控作用，为circRNA水平的m6A修饰研究开启了新篇章。该研究发现circRNA含有大量共有m6A基序，且在翻译起始因子eIF4G2和m6A阅读蛋白YTHDF3介导单个m6A位点驱动翻译起始，并被甲基转移酶METTL3/14增强，被去甲基酶FTO抑制。研究发现circRNA m6A修饰在结直肠癌[22]和肝癌[23]发生发展中也具有重要调控作用，m6A修饰诱导circ1662剪接与表达可加速YES关联蛋白1重组蛋白核转运，从而促进结直肠癌细胞侵袭和迁移；hsa_circ_0007456通过与hsa-miR-139-5p结合促进YTHDF1表达，从而促进HCC细胞增殖。值得注意的是，Chen等[13]在结直肠癌肝转移中发现了m6A甲基化可促进circRNA的核输出，circNSUN2通过YTHDC1与IGF2BP2从细胞核输出到细胞质，增强下游靶基因HMGA2的mRNA稳定性，促进结直肠癌细胞侵袭性，此研究结果为结直肠癌提供了一个潜在的治疗靶点circNSUN2。近年来研究发现circRNA m6A修饰还在宫颈癌、乳腺癌、肺癌、膀胱癌、下咽鳞癌、肺动脉高压和胃癌等恶性肿瘤的发生和进展中发挥重要调控作用[24]。

5　circRNA m6A甲基化修饰在口腔领域的研究现状

目前，circRNA水平的m6A甲基化修饰在口腔方向的文献极少，研究仅限于在成釉细胞瘤和口腔种植骨吸收方向初步研究。Niu等[25]首次提供了人类成釉细胞瘤的m6A修饰表达谱全景观，认为m6A修饰影响长链非编码RNA和circRNA的加工，并鉴定了具有高甲基化或低甲基化m6A修饰的差异表达的mRNA，这可能有助于观察m6A介导的基因表达调控机制。在口腔种植方向，RNA甲基化酶METTL3作用于成骨细胞外泌体中circ_0008542的m6A功能位点，促进circ_0008542与miRNA-185-5p的竞争结合，导致靶基因RANK（receptor activator of NF-kB）的增加和破骨细胞骨吸收的启动；而RNA去甲基化酶ALKBH5抑制circ_0008542与miRNA-185-5p的结合，从而纠正骨吸收过程，提示可使用释放ALKBH5的外泌体增强即刻种植体的抵抗力[26]。

此外，口腔扁平苔藓组织异常表达的circRNAs表达谱已构建，表明circRNA在OLP的发病机制中发挥了重要作用[27]。Xu等[28]发现circRNA在口腔潜在恶性疾病——口腔白斑（oral leukoplakia，OLK）中发挥重要作用，构建了OLK circRNA表达谱并对OLK中的差异circRNA进行了全面的生物信息学分析，源于人白细胞抗原-C（human leukocyte antigen-C，HLA-C）的circHLA-C是一种很有前景的诊断生物标志物，具有作为OLK治疗性遗传

靶点的潜力；Hsa_circ_0060927可作为潜在的关键ceRNA，通过上调三结构域蛋白14（tripartite motif-containing 14，TRIM14）海绵下游miR-195-5p并促进OLK癌变，Hsa_circ_0060927有望成为通过hsa_circ_0060927/miR-195-5p/TRIM14轴预防和治疗OLK致癌的分子标志物[29]。但circRNA水平的m6A甲基化修饰在口腔恶性及潜在恶性疾病方向的研究仍较少。

m6A修饰与OSCC的发生发展密切相关，其中研究最多的是m6A甲基转移酶METTL3与METTL14在OSCC中的作用，但关于circRNA的m6A修饰在OSCC及口腔潜在恶性疾病中的研究未见报道，因此笔者仅从m6A相关酶在OSCC中的研究阐述m6A甲基化修饰在OSCC中的研究现状。①METTL3是调节OSCC肿瘤发生的关键因素，通过YTHDF1介导的m6A修饰增强c-Myc稳定性，促进OSCC发生[30]；METTL3介导的m6A修饰促进BMI1 mRNA翻译并增强OSCC的增殖和转移[31]；METTL3还可通过m6A介导阅读蛋白IGF2BP2结合增强SLC7A11的mRNA稳定性，促进OSCC进展[32]；此外，当OSCC细胞自噬被激活时，METTL14的表达上调，METTL14的高表达可有效降低OSCC的增殖、迁移和侵袭[33]。②m6A去甲基化酶FTO可靶向作用于OSCC中的eIF4G1转录本并调节细胞自噬和肿瘤发生；在雷帕霉素诱导的OSCC自噬细胞中发现，敲低FTO表达后导致eIF4G1下调，同时促进自噬并抑制肿瘤发生[34]；FTO在有咀嚼槟榔习惯的OSCC患者黏膜组织和慢性槟榔碱处理的OSCC细胞系中上调，且FTO在OSCC细胞中受到FOXA2转录因子负调控，表明FTO在槟榔碱诱导的OSCC进展中发挥致癌作用[35]；③m6A阅读蛋白HNRNPL可调节OSCC组织中SRSF3的表达和SRSF3外显子的可变剪接[36]，研究表明HNRNPC可促进OSCC的癌变，可能成为OSCC新的生物标志物和治疗靶点[37]；沉默HNRNPA2B1可通过上皮-间充质转化（epithelial-mesenchymal transition，EMT）抑制OSCC的增殖、迁移和侵袭，HNRNPA2B1可能具有通过LINE-1/TGF-β1/Smad2/Slug信号通路靶向EMT促进OSCC癌变的潜力[38]。

6　小　结

综上所述，circRNA m6A修饰在多种良恶性疾病中发挥重要临床价值，但在口腔领域仅处于初步探索阶段。circRNA m6A修饰在口腔恶性疾病和潜在恶性疾病中的作用有广阔的研究前景，深入探索circRNA m6A修饰在口腔疾病中的调控机制，为口腔恶性疾病及口腔潜在恶性疾病的诊断与治疗提供参考。

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