



miRNA-92a-2-5p 在肿瘤及其他疾病中的研究进展

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摘要: miRNA是一类小的非编码RNA, 通过与信使RNA (mRNA) 中的3' 未翻译区域结合, 来抑制翻译或诱导靶标mRNA的降解来控制基因的表达。而miRNA-92a-2-5p作为miR-106a-363簇的成员, 已有相关研究表明, miRNA-92a-2-5p在细胞增殖、代谢、凋亡、侵袭和免疫等方面发挥着重要的调节作用, 可能是诊断某些疾病的潜在生物标志物。在这里, 我们回顾了目前与miRNA-92a-2-5p相关的研究, 包括其在肿瘤进展中的作用和分子机制, 阐述miRNA-92a-2-5p在生物体的功能作用。

关键词: miRNA-92a-2-5p; 生物标志物; 肿瘤; 免疫

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Research Progress of MirNA-92A-2-5P in Cancer and Other Diseases

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ABSTRACT: Mirnas are a class of small non-coding Rnas that control gene expression by binding to the 3 'untranslated region of messenger RNA (mRNA) to inhibit translation or induce the degradation of target mRNA. As a member of Mir-106A-363 cluster, mirNA-92A-2-5P has been shown to play an important regulatory role in cell proliferation, metabolism, apoptosis, invasion and immunity, and may be a potential biomarker for the diagnosis of some diseases. Here, we review the current studies related to mirNA-92A-2-5P, including its role in tumor progression and molecular mechanisms, To elucidate the functional role of mirNA-92A-2-5P in living organisms.

KEY WORDS: mirNA-92A-2-5P; biomarker; tumor; immunity

0 引言

抽象: miRNA是一类短的非编码RNA, 通常为20-23个核苷酸, miRNA的主要功能是指导基因表达的转录后调控, 通常是通过与同源mRNA的3' 未翻译区域 (UTR) 结合并抑制其翻译或稳定性^[1-2]。而miR-17-92簇是一个高度保守的基因簇, 也称OncomiR-1, 在脂肪细胞分化^[3], 血管生成^[4], 肿瘤发生^[5], 包括在心脏发育^[6-7]等方面都发挥着重要作用。

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17-92含有多顺电子启动子, 位于人类染色体13q31.3和C13orf25基因的第三内含子上^[8], 这是第一个miRNA癌基因^[9], 含有6个成员, 包括miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1和miR-92a和两个旁系簇miR-106a和miR-106b^[10], 而miR-106a-363簇是位于X染色体上, 编码着miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92a-2, miR-363^[11]。miRNA-92a-2-5p作为miR-106a-363簇成员, 在细胞增殖、代谢、凋亡、侵袭和免疫等方面

发挥着重要的调节作用，可能是诊断某些疾病的潜在生物标志物。

1 miRNA-92a-2-5p与肿瘤的关系

1.1 miRNA-92a-2-5p与肝细胞癌

肝细胞癌（HCC）是世界上第五大最常被诊断出的肿瘤，也是癌症死亡的第三大原因^[12]。外泌体由包括巨噬细胞在内的多种细胞分泌，并且可以从巨噬细胞迁移到肿瘤细胞，以促进肿瘤进展、侵袭和转移^[13-14]。在2020年，Liu G^[15]等人研究证明了巨噬细胞通过外泌体将miR-92a-2-5p传播给肝癌细胞，以增加肝癌的侵袭能力。并且通过靶向AR mRNA的3' UTR抑制AR翻译，改变PHLPP/p-AKT/ β -连环蛋白信号传导实现的。同时，Liu G等人通过分析了TCGA数据库中HCC临床样本中的miR-92a表达以及ENCORI泛癌分析平台的数据，证实了肿瘤组织中miR-92a的表达增加，而低表达miR-92a-2-5p的肝细胞癌（HCC）患者比高表达的miR-92a-2-5p的患者具有更长的生存时间，这表明了miR-92a-2-5p功能在体内的重要性。

1.2 miRNA-92a-2-5p与肾细胞癌

肾细胞癌（RCC）是人类泌尿系统的常见恶性肿瘤，也是泌尿系统肿瘤患者死亡的第二大原因，约占所有成人恶性肿瘤的3%^[16-17]，2021年，Ling Gao^[18]等人研究显示，在RCC细胞中KLLN是miR-92a-2-5p的直接靶标，一种环状RNA（circAMOTL1L）可通过miR-92a-2-5p上调KLLN表达，在肾癌细胞中能够抑制细胞增殖，促进体外细胞凋亡，抑制体内肿瘤生。而过表达miR-92a-2-5p促进了肾细胞癌（RCC）细胞的增殖并抑制了细胞凋亡。揭示了可能是通过circAMOTL1L-miR-92a-2-5p-KLLN调节轴在肾细胞癌（RCC）中发挥作用，从而抑制肾细胞癌（RCC）生长。

1.3 miRNA-92a-2-5p与乳腺癌

乳腺癌（BC）是乳腺癌是女性中最常见

的癌症，也是全球女性癌症相关死亡的主要原因^[19]。2018年，Minghui Li^[20]等人一项研究显示乳腺癌（BC）患者的血浆样本中的miR-92a-2-5p显著上调，同时Minghui Li等人分析与临床病理参数（TNM分期，组织学分级，ER和HER2状态）的相关性。结果表明I+II级疾病患者miR-92a-2-5p显著高于III级疾病患者，ER阳性患者的血浆miR-92a-2-5p水平显著高于ER阴性患者。血浆中来自miR-106a-363簇的miR-92a-2-5p，也可用作新型无创生物标志物用于乳腺癌（BC）检测。

1.4 miRNA-92a-2-5p与胰腺癌

胰腺癌（PC）是最致命的恶性肿瘤之一，是世界范围内的一大健康问题^[17]。患者的5年生存率仅为5%-10%，中位生存时间为诊断后5-6月^[21-22]。2020年Alizadeh Savareh B^[23]等人通过分析四个GEO微阵列数据集，使用与胰腺癌相关的生物信息学方法确定了循环miRNA的列表，利用由粒子群优化（PSO）+人工神经网络（ANN）和邻域分量分析（NCA）迭代组成的组合方法，一项由miR-663a、miR-1469、miR-92a-2-5p、miR-125b-1-3p和miR-532-5p组成最终模型，对调查的病例和验证集显示出很好的诊断结果，该miRNA指数可以作为非侵入性和潜在的PC诊断模型。

1.5 miRNA-92a-2-5p与小细胞肺癌

肺癌仍然是肺癌是全球发病率第二、致死率第一的肿瘤^[24]，虽然大多数SCLC患者最初对细胞毒性化疗有反应，但不可避免地会出现耐药性，五年生存率令人沮丧的^[25]。在2010年，Ranade AR^[26]等人研究显示的小细胞肺癌的miR-92a-2*表达水平增高与化学耐药性和SCLC患者的生存率降低有关，肿瘤miR-92a-2*可能应用于筛查有从头化学耐药风险的SCLC患者。另一项关于miRNA-92a-2-5p与小细胞肺癌研究表明，SCLC患者组血浆miR-92a-2水平明显高于健康对照组，ROC曲线分析显示，SCLC诊断的特异性和敏感性分别

为100%和56%，ROC曲线下面积（AUC）为0.761，miR-92a-2-5p可作为小细胞肺癌的生物标志物^[27]。

1.6 miRNA-92a-2-5与非肌肉浸润性膀胱癌

膀胱癌是尿路中最常见的癌症，在恶性肿瘤的发病率中排名第10位^[28]。在所有新诊断的膀胱癌患者中，约75%-80%为非肌肉浸润性膀胱癌（NMIBC）^[29]。2018年，He YH^[30]等人研究证明了NMIBC患者LAMC3和KIT的表达显著降低，KIT和LAMC3可能通过多种miRNA（如has-miR-92a-2-5p）调控lncRNA，最终在NMIBC癌症的发展中发挥了作用。

1.7 miRNA-92a-2-5与卵巢颗粒细胞瘤

卵巢颗粒细胞瘤是一种低级别肿瘤，分为成人型和幼年型两种病理类型。2021年，Liu J^[31]等人研究发现，通过人卵巢颗粒细胞肿瘤系（COV434细胞系）miRNA敲低模型，miR-92a-2-5p调控了Bcl2介导的镉（Cd）对卵巢颗粒细胞的凋亡效应。潜在的机制可能涉及对miR-92a-2-5p介导的Bcl2基因调控。另一项Sun Y^[32]等人研究表明镉（Cd）暴露显著上调了成年雌性小鼠卵巢GCs中miR-92a-2-5p的表达，显著下调了抗凋亡基因Bcl2的表达水平，同时，证实miR-92a-2-5p与Bcl2 3' UTR直接结合，参与大鼠卵巢颗粒细胞（GC）的凋亡，可能通过影响C-myc的表达参与了miR-92a-2-5p的转录调控过程。

2 miRNA-92a-2-5p与免疫的关系

近年来，研究表明，microRNA（miRNA）可以调节先天免疫反应^[33-34]，SARS-CoV-2在2020年引起COVID-19大流行^[35-36]。2022年，Miyashita Y^[37]等人用BNT162b2（COVID-19疫苗）进行了前瞻性队列研究，研究表明了血清中的EV miR-92a-2-5p水平与不良反应的程度呈负相关，miR-92a-2-5p预计与接种BNT162b2疫苗后的免疫反应

相关。另一项Ji C^[38]等人对感染副溶血性弧菌的斑马鱼幼虫的相关miRNA和mRNA转录组进行了研究，证明了miR-92a-2-5p在感染副溶血性弧菌的斑马鱼幼虫的表达是显著下调，可能通过调节靶基因在先天免疫应答中发挥重要作用。

3 miRNA-92a-2-5p在心脑血管中的研究

心血管疾病（CVDs），主要是缺血性心脏病和中风，主要是缺血性心脏病（IHD）和中风，是全球死亡的主要原因，也是导致残疾的主要原因^[39]。miRNA相关的基因序列多态性在神经系统疾病、心血管疾病的发展中发挥了重要作用^[40]。在2019年，刘秀贤^[41]等人一项关于血清微核糖核酸miR-92a-2-5p表达水平与中风后抑郁的相关性的研究，结果表明了老年卒中患者血清miR-92a-2-5p表达增高，且可增加老年卒中后抑郁风险。2019年，Li H^[42]的研究显示了miR-92a-2-5p能够易位到线粒体中以抵消线粒体基因细胞色素-b（mt-Cytb）下调，重组腺相关病毒（rAAV）介导的miR-92a-2-5p可以通过可增强线粒体翻译，减少活性氧（ROS）产生和脂质沉积来挽救db/db小鼠心脏的心脏舒张功能障碍，最终挽救糖尿病性心肌病。2021年，Kong LY^[43]研究显示在氧气-葡萄糖剥夺和再氧合（OGD / R）暴露细胞中rno-miR-92a-2-5p的表达水平降低，miR-92a-2-5p可能参与了间充质干细胞来源的外泌体对脑微血管内皮细胞中氧-葡萄糖剥夺和复氧诱导的细胞损伤的保护作用。

4 miRNA-92a-2-5p在其他方面中的研究

miRNA-92a-2-5p不仅在肿瘤、免疫以及神经系统方面的有着较大的调控作用，miRNA-92a-2-5p在生物体中其他方面也有着相应的调节作用。2019年，Zhao Y^[44]的一项研

究发现Mmu-miR-92a-2-5p在日本血吸虫诱导的肝纤维化过程中下调, mmu-miR-92a-2-5p可以通过靶向TLR2降低肝纤维化相关蛋白的表达并调节细胞活力, 从而预防日本血吸虫诱导的肝纤维化。而Long CY^[45-46]等人的研究表明, miR-92a-2-5p在肛门直肠畸形(ARM)胎儿中异常过度表达的。过表达miR-92a-2-5p后, 其直接靶基因PRKCA表达下调, 抑制了细胞增殖和增加细胞凋亡。进一步揭示了miR-92a-2-5p在ARM过程中通过负调控PRKCA, 异常的miR-92a-2-5p / PRKCA / β -连环蛋白信号传导可能通过抑制增殖和诱导肠上皮细胞凋亡来促进肛门直肠畸形的形成。

5 总结与展望

MicroRNA (miRNA) 是一种小分子RNA, 作为癌基因或抗癌基因, 它们被发现在广泛的基本生物学过程中起着至关重要的作用, 参与许多细胞过程, 如增殖、发育、分化、凋亡和肿瘤生长^[47-49]。miR-17-92簇作为一类有着功能的miRNA, 根据序列同源性和种子保存, 可以分为四个miRNA家族: miR-17家族(miR-17-5p, miR-20a, miR-20b, miR-106a, miR-106b, miR-93); miR-18家族(miR-18a, miR-18b); miR-19家族(miR-19a, miR-19b-1和miR-19b-2)和miR-92家族(miR-92a-1, miR-92a-2, miR-25, miR-363)^[10-11]。而miR-92a-2-5p的miRNA与miR-92a共享相同的种子序列, 这表明它们的功能是高度相关的, miR-92a-2编码在X染色体上的miR-106-363簇中, 区域q26.2, Kis2 ncRNA是它们的pri-miRNA^[50]。miRNA-92a-2-5p在生物体中的各个方面有着相应的调节作用, 如上述所言miRNA-92a-2-5p可以参与调节免疫反应, 保护心脏舒张功能, 增加老年卒中后抑郁风险, 降低肝纤维化等。并且已有各项实验研究证明了miR-92a-2-5p对肿瘤发生的贡献作

用, miR-92a-2-5p表达水平与肿瘤患者的生存率存在一定相关性, 潜在机制主要包括抑制或促进肿瘤细胞增殖、凋亡、侵袭转移等, 并有望可作为某些肿瘤的潜在生物标志物。尽管已经做了一些研究来检查靶标(如Bcl2)以及与关键肿瘤原癌基因(如KLLN、KIT)以及和肝细胞癌(HCC)相关的信号通路(PHLPP/p-AKT/ β -连环蛋白信号)的相互作用, 对miR-92a-2-5p在肿瘤作用中的生物学功能和作用有所了解, 但还需要做更多的工作来充分了解miR-92a-2-5p的调节和作用, 以及进一步了解miR-92a-2-5p的机制及其在肿瘤中的靶基因。

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