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Роль микроРНК в канцерогенезе немелкоклеточного рака легкого

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АННОТАЦИЯ

Введение. Рак легкого является самым распространенным злокачественным новообразованием. Несмотря на большие достижения в таргетной терапии, иммунотерапии и химиотерапии, немелкоклеточный рак легкого остается основной причиной смерти от рака во всем мире. Развитие опухоли — сложный процесс, на который могут влиять как факторы окружающей среды, так и генетическая предрасположенность. Хотя онкогенные факторы широко изучены, основные механизмы, способствующие онкогенезу, в настоящее время остаются невыясненными. Таким образом, исследования онкогенных механизмов, в т. ч. с вовлечением микрорибонуклеиновой кислоты (миРНК) являются важными для диагностики и лечения злокачественных новообразований. МиРНК — это класс малых некодирующих рибонуклеиновых кислот, которые участвуют в разнообразных клеточных биологических процессах, включая эпителиально-мезенхимальный переход, апоптоз, пролиферацию, инвазию и метастазирование раковых клеток. В недавно опубликованных работах показано, что характер течения онкологического заболевания можно спрогнозировать путем анализа уровня экспрессии некоторых миРНК. Таким образом, миРНК являются перспективной диагностической и терапевтической мишенью при онкологических заболеваниях.

Заключение. В настоящем обзоре обобщены данные о роли в канцерогенезе и прогностической значимости ряда миРНК: миРНК-128, миРНК-4500, миРНК-222, миРНК-224, миРНК-124, миРНК-1256, миРНК-127, миРНК-129-2, миРНК-137 и миРНК-375, — при немелкоклеточном раке легкого.

Ключевые слова: *микроРНК; миРНК; немелкоклеточный рак легкого; канцерогенез; диагностическая значимость; прогностическая значимость*

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ЭКО•ВЕКТОР

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Role of Microribonucleic acid in the Carcinogenesis of Non-Small-Cell Lung Cancer

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ABSTRACT

INTRODUCTION: Lung cancer is the most common malignant neoplasm. Despite advances in target therapy, immunotherapy, and chemotherapy, non-small cell lung cancer remains the major cause of cancer-related death worldwide. Tumor development is a complex process that depends on the influence of environmental factors and genetic predisposition. Although oncogenic factors have received much attention, the main mechanisms for oncogenesis are still poorly understood. Thus, studying the oncogenic mechanisms, including those with the involvement of microribonucleic acid (microRNA), is important for the diagnostics and treatment of malignant neoplasms. MicroRNA (miRNA) belong to the class of small non-coding ribonucleic acids that are involved in various cellular biological processes, including epithelial–mesenchymal transition, apoptosis, proliferation, invasion, and metastatic dissemination of cancer cells. Recent publications show that the course of the oncological disease can be predicted by evaluating the expressions of some miRNAs. Therefore, miRNAs serve as promising diagnostic and therapeutic targets in oncological diseases.

CONCLUSION: This review summarizes data on the role in carcinogenesis and prognostic significance of several miRNA (i.e., miRNA-128, -4500, -222, -224, -124, -125b, -127, -129-2, -137, and -375) in non-small cell lung cancer.

Keywords: *microRNA; miRNA; non-small cell lung cancer; carcinogenesis; diagnostic significance; prognostic significance*

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MicroRNA在非小细胞肺癌癌变中的作用研究

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摘要

绪论：肺癌是最常见的恶性肿瘤。尽管在靶向治疗、免疫治疗和化疗方面取得了巨大进展，但非小细胞肺癌仍然是全球癌症死亡的主要原因。肿瘤的发展是一个复杂的过程，可受环境因素和遗传易感性的影响。虽然致癌因子已被广泛研究，但其主要作用机制目前尚不清楚。因此，研究包括微小RNA（miRNA）在内的致瘤机制对恶性肿瘤的诊断和治疗具有重要意义。微小RNA是一类小的非编码核糖核酸，参与多种细胞生物学过程，包括肿瘤细胞的上皮-间充质转化、凋亡、增殖、侵袭和转移。最近发表的论文表明，可以通过分析一些微小RNA的表达水平来预测癌症的病程。因此，微小RNA是一个很有前途的诊断和治疗肿瘤疾病的目标。

结论：本综述总结了一些微小RNA在非小细胞肺癌中的致癌作用和预后意义：miR-128、miR-4500、miR-222、miR-224、miR-124、miR-125b、miR-127、miR-129-2、miR-137和miR-375。

关键词：微小RNA；miRNA；非小细胞肺癌；致癌作用；诊断意义；预后的意义

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略语表

DNA — 脱氧核糖核酸
miRNA — 微小RNA
mRNA — 信使核糖核酸
NSCLC — 非小细胞肺癌
pri-miRNA — miRNA初级转录本
RNA — 代表核糖核酸
EGFR — 表皮生长因子受体
ERα — 雌激素受体α
VEGF — 血管内皮生长因子

绪论

肺癌是最常见的恶性肿瘤。尽管在靶向治疗、免疫治疗和化疗方面取得了巨大进展，但非小细胞肺癌（NSCLC）仍然是全球癌症死亡的主要原因。

肿瘤的发展是一个复杂的过程，可受环境因素和遗传易感性的影响。虽然致癌因子已被广泛研究，但其主要作用机制目前尚不清楚。因此，研究包括微小RNA（miRNA）在内的致瘤机制对恶性肿瘤的诊断和治疗具有重要意义。

目的是分析和总结一些miRNAs在非小细胞肺癌的致癌和预后中的作用的数据：miR-128、miR-4500、miR-222、miR-224、miR-124、miR-125b、miR-127、miR-129-2、miR-137和miR-375。

1993年，由Viktor Ambrosov领导的一组研究人员首次发现了miRNA[1]。现在人类基因组中已经确定了大约2700个miRNAs，它们调节着30%的基因的功能；它们在miRbase.org的数据库中被描述。近年来的研究表明，miRNA参与了人体的许多过程，包括胚胎发育、细胞分化、增殖和凋亡[2,3]。

2002年，由G. Calin教授领导的一组科学家证实了微小RNA和肿瘤过程之间存在联系。他们首次在miR-15a和miR-16-1基因中发现了高频率的缺失，从而得出结论，miRNA具有癌抑制因子的功能。随后，miR-15a和miR-16-1已被证明针对参与细胞周期调节（ANXA1和CDK1）和凋亡（HSPA5和BCL2）的miRNA。随后发表了一篇关于miRNA在癌形成中的作用的研究[4]。目前，人们认为miRNA具有致癌或抑癌特性。致癌miRNA导致细胞增殖、侵袭、血管生成和/或凋亡活性降低，并抑制细胞分化。抑癌miRNA抑制恶性细胞的生长和迁移，促进细胞凋亡的诱导。

研究表明，哺乳动物的miRNA基因位于不同的基因组区域，包括内含子中miRNA的基因间和基因内非编码区，有时也位于基因的外显子中。成熟miRNA的生物发生始于核糖核酸聚合酶II（RNA）对被称为miRNA初级转录本（pri-miRNA）的长非蛋白初级RNA转录本的加工。在通过exportin 5（XPO5）将引物转移到细胞质后，它们与来自RNase III（DICER）家族的核糖核酸酶和RNA诱导的沉默复合物（RISC）结合。尽管miRNA的功能是一个成熟的过程，但可能的变化可以促进肿瘤疾病的发展。许多研究表明，在癌细胞中可以观察到DICER、DROSHA和AGO2基因的变化。2005年，Karube Y.等人对DROSHA和DICER基因表达的抑制在包括肺癌在内的多种癌症中都有记录。上述过程通常与癌症的不良预后有关。

除了肿瘤自身的生物发生变化外，其微环境也会直接影响miRNA的水平。结果表明，这些变化在低氧状态下均可发生[5]。特别是，研究发现，由于缺氧导致DROSHA和DICER水平下降，从而导致癌细胞中miRNA活性的抑制[6]。

尽管生物发生缺陷和miRNA功能活性的整体抑制，在各种形式的癌症中，所谓的致癌miRNA的含量显著增加[7]。肿瘤疾病中介导致癌miRNA表达激活的机制多种多样，并依赖于特定的miRNA。

以下是一些在非小细胞肺癌发生中发挥重要作用的miRNA的最新信息。

miRNA-128

MiRNA-128参与上皮-间充质转化，通过各种靶点影响促进肿瘤生长，并调控癌细胞的凋亡和分化[8]。因此，miRNA-128在结直肠癌中抑制细胞增殖[9]，在非小细胞肺癌中阻断细胞周期[10]。MiRNA-128表达的抑制伴随着血管内皮生长因子（VEGF）表达的增加，从而导致癌细胞转移的增加。同时，miRNA-128过表达可通过作用于NIK2诱导肺癌细胞凋亡。NEK2是苏氨酸激酶家族的一员，在结构上与有丝分裂调节因子NIMA连接[11]，与中心粒富集，其过表达与疾病的耐药性和不良预后相关[12]。D. Zhao等人的研究结果表明，miRNA-128通过直接作用于NIMA-相关激酶2促进肺癌细胞凋亡。作者表明，miRNA-128能诱导肺癌细胞的凋亡，并调节凋亡相关蛋白Bax、裂解caspase-3和Bcl-2的表达。因此，NEK2作为miRNA-128在肺癌细胞中的靶点，NEK2的过表达可阻止miRNA-128促凋亡作用的表现[13]。因此，NEK2在癌症治疗中是一个很有前途的治疗靶点。

miRNA-4500

MiRNA-4500的检测采用高通量测序技术。目前已知miRNA-4500由16个核苷酸组成，位于13号染色体上。Zhang L.等人证明，非小细胞肺癌肺组织中miRNA-4500的含量低于正常细胞。MiRNA-4500的低水平表达通过影响其靶基因LIN28B、NRAS和STAT3的mRNA，促进肿瘤的生长[14]。在Z. Li等人的体外工作中，发现miRNA-4500参与细胞增殖、迁移、侵袭和凋亡。

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因此，我们得出结论，miRNA-4500在非小细胞肺癌的进展中发挥调控作用，是一个有希望的肺癌的诊断和预后标志物[15]。

miRNA-222

最初，miRNA-222被证明能诱导上皮性卵巢癌中肿瘤相关巨噬细胞的极化[16]。进一步的研究表明，miRNA-222-3p通过抑制雌激素受体α（ERα）促进癌的生长和侵袭。许多作者已经表明，miRNA-222-3p的高水平表达与较差的预后[17]和非小细胞肺癌[18]的无复发病程时间相关，并且通过抑制肿瘤抑制因子BBC3与非小细胞肺癌的起始和发展相关。MiRNA-222-3p/BBC3相互作用的生物学意义有待进一步研究。识别和表征它们的功能串扰将有助于理解非小细胞肺癌的发病机制。

miRNA-224

目前，有证据表明，一些miRNA既可以作为癌基因，也可以作为肿瘤抑制因子。这种具有双重功能的分子包括miRNA-224。与此同时，作用的方向在很大程度上取决于癌症的具体类型。特别是，miRNA-224在许多实体肿瘤中被激活，包括肝细胞癌[19]和乳腺癌[20]。有时，miRNA的双重功能取决于靶基因，例如，在前列腺癌中，当与靶基因API5、SMAD4、PHLPP1、PHLPP2和RKIP的mRNA相互作用时，具有致癌作用，而与靶基因TPD52和/或TRIB1相互作用时，具有抑癌作用[21]。我们认为miRNA-224高水平表达与顺铂耐药和预后不良有关。然而，也有研究表明miRNA-224的高表达与预后良好的相关[22]。值得注意的是，miRNA-224的过表达通过与靶基因TNFAIP1和SMAD4的mRNA相互作用，促进肺癌细胞的迁移、侵袭和增殖。得到的数据表明miRNA-224在肺癌进展和转移中的重要作用，这与Wang H. et al.的结果一致[23]。因此，未来miRNA-224的临床诊断可能是确定肺癌患者适当治疗策略和预后的一种补充方法。

miRNA-124-3p

MiRNA-124-3p在基因组中有三个位点：MIR124-1 (8p23.1)、MIR124-2 (8q12.3)和MIR124-3 (20q13.33)，是神经组织特异性分化和神经发生过程的调节因子，在神经系统组织中活跃表达。MiRNA-124表达的抑制在许多类型的癌症中都很常见，包括非小细胞肺癌[24]。miRNA 124a-3在非小细胞肺癌中的靶基因包括：TXNRD1、LHX2、MGAT5、STAT3等，与肿瘤的发生发展、放化疗敏感性相关。例如，Q. Yang等人的一项研究的结果表明，miRNA-124在非小细胞肺癌细胞和组织中的表达往往降低，与LHX2（LIM-homeobox, domain 2）的表达呈负相关，而LHX2在非小细胞肺癌细胞和组织中的表达增加。值得注意的是，miRNA-124在A549和H1299细胞株中的过表达抑制了细胞的迁移和侵袭能力。本研究结果证实miRNA-124过表达和/或LHX2沉默可能为晚期非小细胞肺癌提供一种治疗策略[25]。

此外，miRNA-124与多种肿瘤的耐药相关，包括胃癌[26]和乳腺癌[27]，这显然是通过抑制编码N-乙酰氨基葡萄糖转移酶V的MGAT5靶基因的mRNA表达，影响肿瘤细胞的转移和化疗免疫而介导的[28]。在Cai J.等人已有研究表明，miR-124-3p表达的恢复可抑制FGF2-EGFR通路，增加肺腺癌细胞对培美曲塞的敏感性[29]。因此，miRNA-124-3p是肺腺癌治疗中克服耐药的潜在治疗靶点。

miRNA-125b

MiRNA-125b在人类基因组中有两个位点：MIR125B1 (11q24.1)和MIR125B2 (21q21.1)。这些基因的特征是在5'端不超过1500对核苷酸的地方存在一个CpG岛。MiRNA-125b在维持神经[30]和造血[31]胚胎干细胞的稳态和分化中发挥重要作用。根据特定的环境，miRNA-125b可以调控分化和侵袭的过程，以及凋亡。例如，miRNA-125 b1的过表达抑制了S1PR1基因miRNA的表达，抑制了非小细胞肺癌细胞的增殖、侵袭和迁移。该miRNA的靶基因包括凋亡相关基因BAK1、MCL1、BCL2、SIRT和调节细胞周期和转移的基因TP53INP1、MMP13、KLC2。此外，肺癌患者化疗和手术后血浆中miRNA-125b水平高于未接受治疗的患者。这表明循环miRNA-125b可以成为抗肿瘤治疗的预后生物标志物[32]。

miRNA-127

MiR-127基因定位于14q32.2位点，编码miRNA-127，参与调控肺形成相关基因的表达，以及凋亡的调控。多项研究表明，miR-127过表达可通过与癌基因MAPK4、SKY、BCL6相互作用，抑制胃癌、乳腺癌、胶质母细胞瘤细胞系的细胞增殖，阻断细胞周期、细胞迁移和侵袭[33,34]。与此同时，有研究表明miR-127表达的增加与淋巴结转移的形成有关，例如宫颈癌。因此，miR-127既可以作为抑制基因，也可以作为癌基因。在Shi L.等人的研究中，miRNA-127过表达与肺腺癌相关，并与不良预后相关。MiRNA-127表达水平的增加导致癌细胞从上皮表型向间充质表型的显著转移，这种转移与干细胞性状的出现以及对表皮生长因子受体（EGFR）抑制剂的耐药性增加有关。相反，抑制miRNA-127的表达能逆转这种恶性转变。在同样的研究中，发现了自反馈回路，包括NF-kB（核转录因子-kB）、miRNA-127和TNFAIP3（肿瘤坏死因子α诱导蛋白3基因），它在肺癌中提供了这种侵袭性的上皮-间质转化[35]。因此，这项研究确定了一种新的分子机制，将干细胞、恶性肿瘤和炎症联系起来，为癌症治疗开辟了新的可能性。

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miRNA-129-2

MiRNA-129-2由基因内位点11p11.2（主基因—EST）表示。MiRNA-129的表达在各种类型的肿瘤中均有抑制，包括肺腺癌[36]，而在视网膜母细胞瘤中，miRNA-129的表达增加了[37]。在肺腺癌细胞培养中诱导过表达MIR129-2基因导致有丝分裂在G1/S期停止，随后细胞死亡。与此同时，该miRNA的靶点是Cdk6。非小细胞肺癌侵袭转移增加的控制机制仍未得到充分的研究。因此，miRNA-129表达水平显著下降，而磷酸化的EGFR和MMP9蛋白水平显著升高，与邻近正常组织相比，负责非小细胞肺癌转移。在对肺癌细胞株A549的研究中发现，阻断细胞侵袭和迁移的可能机制是通过抑制靶基因SOX4的miRNA-129基质RNA（mRNA）[38]。因此，miRNA-129、EGFR、SOX4和MMP9似乎是有希望的预防非小细胞肺癌转移的治疗靶点。

miRNA-137

MIR137基因 (1p21.3)位于不编码该蛋白的MIR137HG基因内，CpG岛包括启动子区、MIR137基因本身和MIR2682基因。MiRNA-137是神经组织分化和增殖过程的重要调控因子，是干细胞发育途径的调控因子。MiRNA-137表达的抑制被认为是许多类型的肿瘤，包括非小细胞肺癌。有研究表明，miRNA-137表达的恢复抑制Cdc42和Cdk6，诱导细胞周期阻滞在G1期，导致体内外细胞生长显著下降[39]。在其他的研究中，它被证明导致了凋亡的诱导[40]，在其他的研究中，它被证明通过作用于靶基因SLC22A18（англ.: solute carrier family 22 member 18）的mRNA来抑制NSCLC细胞的侵袭和迁移[41]。更重要的是，miRNA-137在非小细胞肺癌肿瘤组织中的表达下降与恶性肿瘤患者的肿瘤进程严重阶段、远处转移的发展和不良预后相关[42]。

对化疗的耐药性常常导致肿瘤的发展。然而，其潜在的分子机制仍知之甚少。Shen H.等人结果表明，miRNA-137在非小细胞肺癌组织和耐药细胞株A549/紫杉醇（A549/PTX）、A549/顺铂（A549/CDDP）中表达水平较A549非小细胞肺癌细胞降低。此外，miRNA-137的抑制在A549细胞中显著促进细胞生长、迁移、存活和细胞周期G1/S期的过渡[43]。在另一项研究中，使用顺铂治疗的非小细胞肺癌患者的组织样本中miRNA-137的表达明显低于健康组织样本。MiRNA-137高表达的非小细胞肺癌患者的无复发生存率和总生存率高于miRNA-137低表达的非小细胞肺癌患者的生存率。因此，本研究的结果表明，miRNA-137可抑制非小细胞肺癌患者的肿瘤生长，并增加对顺铂的敏感性。可以假设miRNA-137可能是非小细胞肺癌患者独立的良好预后因素，有助于未来新的治疗策略的发展。

miRNA-375

关于肿瘤中MIR375基因表达变化的文献数据是不明确的，显然，不同类型的癌症具有特异性。因此，在宫颈癌中，该基因的表达水平降低了[44]。在ERα+乳腺癌细胞株中miRNA-375的高表达与组蛋白H3K9me2甲基化缺失和DNA局部低甲基化有关，miRNA-375的抑制导致增殖暂停。MiRNA-375在肺腺癌和小细胞肺癌中的表达也增加[45]。根据其他作者的研究，在非小细胞肺癌中，miRNA-375的表达下降[46]。因此，Cheng L.等人的研究表明，miRNA-375在非小细胞肺癌细胞中的表达显著降低，诱导miRNA-375表达可通过触发非小细胞肺癌细胞凋亡抑制其增殖[47]。另一项研究显示，VEGF和MMP-9的过表达与miRNA-375的低表达有关，这是导致非小细胞肺癌患者预后不良的原因。

因此，miRNA-375既可以作为非小细胞肺癌的潜在治疗靶点，也可以作为脑转移的预测性生物标志物和非小细胞肺癌的独立预后因素。

结论

这些数据表明，微小RNA属于小的非编码核糖核酸类，在人体中负责实现各种过程：胚胎发育、细胞分化、增殖、凋亡。近年来的研究证明了微小RNA与癌变之间存在一定的关系。已经证实，微小RNA可以具有致癌或抑癌特性。致癌微小RNA促进细胞增殖、侵袭和血管生成，降低细胞凋亡强度，抑制细胞分化。抑癌微小RNA抑制癌细胞的生长和迁移，促进细胞凋亡的诱导。

在过去的十年中，许多研究结果已经发表，表明微小RNA参与非小细胞肺癌的癌变。有证据表明，一个微小RNA可以具有多个基质微核糖核酸靶点，而多个微小RNA可以作用于同一靶点。研究发现，miRNA-4500、miRNA-224、miRNA-124、miRNA-125b和miRNA-127等微小RNA是肺癌诊断和预后的重要标志物

在本文中，只有一小部分微小RNA在肺癌的肿瘤过程、行为和预后中发挥重要作用。其他微小RNA对非小细胞肺癌的诊断和最佳治疗策略的选择可能的意义还有待进一步研究。然而，已经可以得出结论，在肺癌和其他一些肿瘤疾病患者中，微小RNA是有希望的治疗靶点。

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