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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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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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ECO•VECTOR

LIST OF ABBREVIATIONS

DNA — deoxyribonucleic acid
miRNA — microribonucleic acid
mRNA — matrix ribonucleic acid
NSCLC– non-small cell lung cancer
pri-miRNA — precursor of microribonucleic acid
RNA — ribonucleic acid
EGFR — epidermal growth factor receptor
ERα — estrogen receptor alpha
VEGF — vascular endothelial growth factor

INTRODUCTION

Lung cancer is the most common malignant neoplasm. Despite significant advances in target therapy, immunotherapy, and chemotherapy, non-small cell lung cancer (NSCLC) remains a major cause of death from cancer in the world.

Tumor development is a complex process influenced by environmental factors and genetic predisposition. Although much attention has been given to oncogenic factors, the main mechanisms of oncogenesis remain unexplained. Hence, investigating the oncogenic mechanisms, including those involving microribonucleic acid (miRNA), is essential for diagnosing and treating malignant neoplasms.

This study **aimed** to analyze and systematize the data on the role of several miRNAs (miRNA-128, miRNA-4500, miRNA-222, miRNA-224, miRNA-124, miRNA-125b, miRNA-127, miRNA-129-2, miRNA-137, and miRNA-375) in carcinogenesis and prognosis in NSCLC.

MiRNA was first discovered in 1993 by a group of researchers led by Victor Ambrosov [1]. At present, about 2700 miRNAs are identified in the human genome, which controls 30% of genes; their description is provided in the database on the miRbase.org website. Recent works have shown that miRNA is responsible for many human processes, including *embryonic development, cell differentiation, proliferation, and apoptosis* [2, 3].

The connection between miRNAs and oncological processes was proved in 2002 by a group of scientists led by Professor G. Galin. They first discovered a high frequency of deletions in the miR-15a and miR-16-1 genes and concluded that *miRNAs possess oncosuppressive functions*. Subsequently, it was shown that the targets for miR-15a and miR-16-1 are miRNAs that participate in regulating the cell cycle (*ANXA1* and *CDK1*) and apoptosis (*HSPA5* and *BCL2*). Subsequently, a study on the role of miRNAs in carcinogenesis was published [4]. At present, it is known that *miRNAs possess either oncogenic or oncosuppressive properties*. Oncogenic miRNAs enhance cell proliferation, invasion, angiogenesis, and/or reduce apoptotic activity and suppress cell differentiation. Oncosuppressive miRNAs inhibit the growth and migration of malignant cells and induce apoptosis.

miRNA genes in mammals are located in various genomic regions, including intergenic and intragenic non-coding regions of miRNA in introns and sometimes in the gene exon. Mature miRNA biogenesis begins with processing long non-protein primary RNA transcripts called precursor miRNA (pri-miRNA) by polymerase II of ribonucleic acid (RNA). Pri-miRNA moves into the cytoplasm via exportin 5 (*exportin 5*, XPO5) and binds with ribonuclease of RNase III family (RNase III, DICER) and with RNA-induced silencing complex. Although miRNA functioning is a "well-established" process, likely changes can contribute to the development of oncological diseases. Several studies showed changes in the *DICER*, *DROSHA*, and *AGO2* genes in cancer cells. In 2005, Karube et al. recorded the suppression of *DROSHA* and *DICER* gene expression in many forms of cancer, including lung cancer. The above processes are often associated with a poor prognosis for oncologic diseases.

Besides changes in the biogenesis of the tumor itself, its microenvironment may directly affect the miRNA level. These changes may be induced by hypoxia [5]. In particular, *hypoxia leads to miRNA activity suppression in cancer cells due to reduced DROSHA and DICER levels* [6].

Despite the defects in the biogenesis and global suppression of the functional activity of miRNAs, the content of the so-called oncogenic miRNAs significantly increases in different forms of cancer [7]. Mechanisms that mediate the activation of oncogenic miRNA expression are diverse and depend on a particular miRNA.

The latest information about some miRNAs that play an essential role in *NSCLC* genesis is provided below.

miRNA-128

MiRNA-128 participates in the epithelial to mesenchymal transition, promotes tumor growth by acting on different targets, and modulates apoptosis and differentiation of cancer cells [18]. Thus, miRNA-128 inhibits cell proliferation in colorectal cancer [9] and blocks the cell cycle in NSCLC [10]. Suppression of miRNA-128 expression is accompanied by enhanced expression of vascular endothelial growth factor (VEGF), leading to enhanced metastatic spread of cancer cells. At the same time, miRNA-128 overexpression induces lung cancer cell apoptosis through the action on NEK2. NEK2 is a member of the threonine kinase family, is structurally interrelated with NIMA mitotic regulator, and

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is enriched with centrosomes [11]. Its overexpression is associated with drug resistance and poor prognosis [12]. The results of studies by Zhao et al. demonstrated that miRNA-128 promotes apoptosis in lung cancer by direct action on the NIMA-related kinase 2. The authors showed that miRNA-128 induces apoptosis of the lung cancer cells and regulates the expression of apoptosis-related Bax proteins, cleaved caspase-3, and Bcl different-2. Thus, NEK2 can be a target for miRNA-128 in lung cancer cells, and NEK2 overexpression can prevent the manifestation of the proapoptotic effect of miRNA-128 [13]. Thus, *NEK2 is a promising therapeutic target in the treatment of cancer*.

miRNA-4500

miRNA-4500 was discovered using high throughput sequencing technology. Currently, miRNA-4500 consists of 16 nucleotides and is located on chromosome 13. Zhang et al. demonstrated that the content of *miRNA-4500 in lung tissue in NSCLC is lower than in normal cells*. A low level of miRNA-4500 expression promoted tumor growth by acting on mRNA of its *LIN28B*, *NRAS*, and *STAT3* target genes [14]. Li et al. showed that miRNA-4500 participated in cell proliferation, migration, invasion, and apoptosis in vitro. Subsequently, it was concluded that *miRNA-4500 plays a regulatory role in NSCLC progression and is a promising diagnostic and prognostic lung cancer marker* [15].

miRNA-222

Initially, miRNA-222 was shown to induce tumor-associated macrophage polarization in epithelial ovarian cancer [16]. Further research showed that miRNA-222-3p promotes growth and invasion of carcinoma by suppressing estrogen receptor alpha (ERα). The work of different authors demonstrated that a high level of miRNA-222-3p expression is associated with a worse prognosis [17] and relapse-free course duration in NSCLC [18], and also with initiating and developing NSCLC by suppressing the BBC3 tumor suppressor. The biological significance of the interaction of miRNA-222-3p/BBC3 is the subject of further study. Identification and characteristics of their functional "crosstalk" will help investigators understand the pathogenetic mechanisms of NSCLC.

miRNA-224

Currently, there is evidence that some miRNAs can function either as oncogenes or as tumor suppressors. MiRNA-224 belongs to such molecules that perform a double function. Here, the direction of the effect largely depends on the specific type of cancer. In particular, miRNA-224 is activated in several solid tumors, including hepatocellular carcinoma [19] and breast cancer [20]. Sometimes, the manifestation of the double function of miRNA depends on the target gene. For example, in prostate cancer, it manifests the oncogenic function in the interaction with mRNA of *API5, SMAD4, PHLPP1, PHLPP2,* and *RKIP* target genes, and the oncosuppressive function is manifested in the interaction with *TPD52* and/or *TRIB1* [21]. *A high level of miRNA-224 expression is associated with resistance to cisplatin therapy and poor prognosis. However, high expression of miRNA-224 was also associated with a favorable prognosis* [22]. To note, overexpression of miRNA-224 promotes the migration, invasion, and proliferation of lung cancer cells through interactions with mRNA of *TNFAIP1* and *SMAD4* target genes. The data obtained indicate an essential role of miRNA-224 in the progression and metastatic spread of lung cancer, which agrees with the results of Wang et al. [23]. Thus, the clinical diagnosis of miRNA can be used in the future as a complementary method to determine the appropriate treatment strategies of patients with lung cancer and prognosis.

miRNA-124-3p

miRNA-124-3p is presented in the genome by three loci: *MIR124-1* (8p23.1), *MIR124-2* (8q12.3), and *MIR124-3* (20q13.33). It is a nervous tissue-specific regulator of differentiation and neurogenesis and is actively expressed in tissues of the nervous system. Suppression of miRNA-124 expression is often observed in many cancer types, including NSCLC [24]. The target genes for miRNA-124a-3 in NSCLC are T*XNRD1, LHX2, MGAT5, STAT3,* and others associated with the tumor development and progression and sensitivity to radio- and chemotherapy. For example, a study by Yang et al. showed that miRNA-124 expression frequently decreased in cells and tissues of NSCLC and negatively correlated with LNX2 expression (*LIM-homeobox, domain 2*), which increased in cells and tissues in NSCLC. Overexpression of miRNA-124 in A549 and H1299 cell lines suppressed the migratory and invasive abilities of cells and was confirmed by the results of this study. Overexpression of miRNA-124 and/or the "silence" of LHX2 may provide a therapeutic strategy for advanced NSCLC [25].

miRNA-124 is associated with drug resistance of different tumors, including gastric cancer [26] and breast cancer [27]. This resistance is probably mediated by suppressing mRNA expression of the *MGAT5* target gene that encodes N-acetylglucosaminyltransferase V and plays a role in the metastatic spread of tumor cells and resistance to chemotherapy [28]. The work by Cai, et al. showed that the recovery of miR-124-3p expression might inhibit the FGF2-EGFR pathway and increase the sensitivity of lung adenocarcinoma cells to pemetrexed [29]. Therefore, miRNA-124-3p is a potential therapeutic target for overcoming drug resistance in treating lung adenocarcinoma.

miRNA-125b

It is represented in the human genome by two loci: *MIR125B1* (11q24.1) and *MIR125B2* (21q21.1). These

genes are characterized by the presence of CpG-islet covering no more than 1500 pairs of nucleotides from their 5' ends. MiRNA-125b plays an important role in homeostasis and the differentiation of neural [30] and hematopoietic [31] embryonic stem cells. MiRNA-12e5b can regulate the differentiation and invasion processes and apoptosis, depending on the specific context. For example, overexpression of miRNA-125b-1 suppresses miRNA expression of the *S1PR1* gene and proliferation, invasion, and migration of NSCLC cells. The target genes of this miRNA include apoptosis-associated genes — *BAK1, MCL1 BCL2, SIRT,* and regulator genes of the cell cycle and metastasis — *TP53INP1, MMP13, KLC2.* Besides, patients with lung cancer show elevated miRNA-125b levels in blood plasma after chemotherapy and surgery than untreated patients. All this suggests that circulating miRNA-125b can become a prognostic biomarker in response to antitumor therapy [32].

miRNA-127

The *miR-127* gene is located at the 14q32.2 locus, encodes miRNA-127, and regulates the expression of genes responsible for lung formation and apoptosis. Several studies showed that *miR-127* overexpression inhibits cell proliferation, blocks the cell cycle, cell migration, and invasion in cell lines of gastric cancer, breast cancer, and glioblastoma by interacting with the *MARK4, SKY, BCL6* oncogenes [33, 34]. At the same time, the increased *miR-127* expression is associated with the formation of metastases in lymph nodes, for example, in cervical cancer. Thus, *miR-127* can act both as a suppressor gene and an oncogene. In the work of Shi, et al., overexpression of miRNA-127 was associated with lung adenocarcinoma and correlated with poor prognosis. The increased level of miRNA-127 expression led to a marked shift from an epithelial phenotype to the mesenchymal phenotype of cancer cells. This shift was associated with the appearance of stem cell traits and increased resistance to the epidermal growth factor receptor (EGFR) inhibitor.

In contrast, suppression of miRNA-127 expression reversed this malignant transition. In the same work, a self-sustaining regulatory loop was found, including NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), miRNA-127, and TNFAIP3 (tumor necrosis factor, alpha-induced protein 3), which provides this aggressive epithelial-mesenchymal transition in lung cancer [35]. Thus, this work identifies a *new molecular mechanism linking stem cells, malignancies, and inflammation and uncovers new possibilities for cancer treatment*.

miRNA-129-2

MiRNA-129-2 is presented by the intragenic 11p11.2 locus (gene-host — *EST*). The suppression of miRNA-129 expression was demonstrated in different kinds of cancer, including lung adenocarcinoma [36]. In contrast, in retinoblastoma miRNA-129, its expression is increased [37]. Induced overexpression of the *MIR129-2* gene in lung adenocarcinoma cell culture leads to the arrest of mitosis in the G1/S phase and subsequent cell death. Here, the target for this microRNA is Cdk6. The mechanism underlying the control of enhanced invasion and metastatic spread of NSCLC is not sufficiently investigated. Thus, a significant decrease in the miRNA-129 expression level and a significant increase in the phosphorylated *EGFR* and *MMP9* protein levels in tumor tissues responsible for NSCLC metastasis than in adjacent normal tissue. In work performed on the A549 lung cancer cell line, a probable mechanism for blocking invading and migrating cells is based on the matrix RNA (mRNA) suppression of the *SOX4* target gene by miRNA-129 [38]. Thus, miRNA-129, *EGFR, SOX4,* and *MMP9* appear to be promising therapeutic targets for preventing NSCLC metastasis.

miRNA-137

The *MIR137* (1p21.3) gene is located inside the *MIR137HG* non-protein encoding gene. The CpG-islet includes a promoter region, the *MIR137* gene, and the *MIR2682* gene. MiRNA-137 is an important regulator of the differentiation and proliferation processes in the nervous tissue by regulating stem cell development pathways. The suppression of miRNA-137 expression has been shown in many kinds of neoplasms and NSCLC. Some studies showed that the recovery of miRNA-137 expression suppresses *Cdc42* and *Cdk6* and induces a block of the cell cycle in the G1 phase, leading to significantly reduced cell growth *in vivo* and *in vitro* [39]. In other words, it induces apoptosis [40]. In other studies, it inhibited the invasion and migration of NSCLC cells by acting on the mRNA of the SLC22A18 (solute carrier family 22 member 18) target gene [41]. More importantly, reducing the level of miRNA-137 expression in NSCLC tumor tissues correlated with a severe stage of the tumor process, the development of distant metastases, and a poor prognosis for patients [42].

Resistance to chemotherapy often leads to tumor progression. However, the underlying molecular mechanisms remain understudied. Shen et al. showed that the level of miRNA-137 expression was reduced in NSCLC tissues, A549/paclitaxel (A549/PTX), and A549/cisplatin (A549/CDDP) resistant cell lines than the A549 cell line of NSCLC. In addition, the repression of miRNA-137 significantly promoted cell growth, migration, cell survival, and transition in the G1/S phase of the cell cycle in A549 cells [43]. In another study, miRNA-137 expression in tissue samples of patients with NSCLC processed with cisplatin was noticeably lower than in healthy tissue samples. The relapse-free survival and overall survival of patients with NSCLC demonstrating high miRNA-137 expression were higher than those of

patients with NSCLC demonstrating low miRNA-137 expression. Thus, the results of this study suggest that miRNA-137 inhibits tumor growth and increases the sensitivity of patients with NSCLC to cisplatin. Based on the above, miRNA-137 may be an independent favorable prognostic factor in patients with NSCLC and can be used to develop new therapeutic strategies in the future.

miRNA-375

The literature on changes in the *MIR375* gene expression in tumors is ambiguous and specific for different cancer types. Thus, in cervical cancer, the level of expression of this gene was decreased [44]. In contrast, in ERα-positive cell lines of breast tumors, high expression of miRNA-375 was observed, which is associated with the loss of methylation of H3K9me2 histones and local hypomethylation of deoxyribonucleic acid (DNA). The suppression of miRNA-375 suspends proliferation. miRNA-375 expression increases in lung adenocarcinoma and small cell lung cancer [45]. According to other authors, miRNA-375 expression is decreased in NSCLC [46]. Thus, Cheng et al. showed that the expression of miRNA-375 in NSCLC cells is significantly decreased, and induction of miRNA-375 expression inhibits NSCLC cell proliferation by triggering apoptosis [47]. In another work, overexpression of VEGF and MMP9 was associated with the low level of miRNA-375 expression, which is the basis for a poor prognosis for patients with NSCLC.

Thus, miRNA-375 can be a potential therapeutic target for NSCLC, a prognostic biomarker of brain metastases, and an independent prognostic factor in NSCLC.

CONCLUSION

The given data show that miRNAs refer to a class of small non-coding ribonucleic acids responsible for different human processes, including embryonic development, cell differentiation, proliferation, and apoptosis. Recent works have proved the existence of the link between miRNAs and carcinogenesis. miRNAs can have oncogenic or oncosuppressive properties. The oncogenic properties of miRNAs enhance cell proliferation, invasion, and angiogenesis, reduce the intensity of apoptosis, and suppress cell differentiation. In contrast, oncosuppressive miRNAs inhibit cancer cell growth and migration and promote the induction of apoptosis.

Over the past decades, the results of many studies have been published indicating the involvement of miRNAs in NSCLC carcinogenesis. Convincing evidence indicates that one miRNA can have multiple targets of matrix microribonucleic acid, and several miRNAs can act on the same target. Several miRNAs, including miRNA-4500, miRNA-224, miRNA-124, miRNA-125b, and miRNA-127, are promising prognostic lung cancer markers.

In the presented review, only a few miRNAs were considered that play an essential role in the oncological process, behavior, and prognosis of lung cancer. Further studies have yet to establish the probable significance of other miRNAs for diagnosing and selecting optimal treatment tactics in NSCLC. However, today it is possible to conclude that miRNAs are promising therapeutic targets in patients with lung cancer and several other oncological diseases.

ADDITIONAL INFORMATION

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