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Exosomes and the role of exosomal miRNA in the diagnosis of lung cancer

Abstract. *Exosomes are extracellular vesicles secreted by almost all cell types that can function as a cell-to-cell carrier of information, providing pleiotropic functions in intercellular communication. Exosomes can transport various biomolecules, including proteins and nucleic acids, into recipient cells. The review analyzed the current data on the role of exosomes and the possibility of using exosomal microRNAs as a biomarker in the diagnosis of lung cancer. MicroRNAs can act as oncogenes or tumor suppressors, so they can regulate the expression of genes that play an important role in oncogenesis. At the moment, microRNAs of exosomes are one of the main candidates for the role of molecular markers in liquid biopsy for the diagnosis of oncological diseases. The review analyzes the diagnostic potential of the use of exosomes in carcinogenesis in general, with an emphasis on the use of exosomal microRNAs as biomarkers of lung cancer.*

Keywords: *lung cancer, exosomes; exosomal miRNA; diagnostics; liquid biopsy.*

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Introduction

A necessary condition for the functional activity of any multicellular organism is intercellular interactions, which make it possible to coordinate biochemical and metabolic processes in its cells. Intercellular communication and signaling can be carried out by secreting biologically active molecules into the extracellular space, directly through gap junctions between cells, and by transferring secreted molecules through microvesicular transport through exosomes [1]. In this case, coordinating signals are transmitted using hormones, neurotransmitters, growth factors, cytokines, low molecular weight metabolites, nucleic acids and proteins [2].

Exosomes play an important role in immunity, coagulation, angiogenesis, spermatogenesis, and many various other physiological processes in the organism [3]. Exosomes involved in the processes of intercellular communication function in both paracrine and endocrine modes. Due to its unique structure, which largely resembles a miniature copy of a cell (primarily due to the plasma membrane - a fragment of the cell membrane that reliably isolates exosomes from the external environment), the contents of exosomes remain intact for a long time [4]. Exosomes are now regarded as diagnostic tools and therapeutic agents.

Exosomes were discovered in the mid-1940s [5], but they were first described as extracellular microvesicles in the early 1980s [1]. It was shown that during the maturation of mammalian reticulocytes, the transferrin receptor and some other membrane-bound elements are selectively secreted a cell in extracellular vesicles carried by the bloodstream throughout the body [6]. Exosomes are present in various body fluids such as cerebrospinal fluid, saliva, urine, blood and blood derivatives (serum and plasma) [1,2]. Exosomes contain many different molecules, including proteins, lipids, and various cell metabolites. The complete set of proteins present in exosomes (including thousands of different cellular proteins) is highly variable and reflects the current phenotype of the parent cell. In addition to proteins and lipids, exosomes also contain different classes of nucleic acids: mRNA, microRNA [7], as well as genomic and mitochondrial DNA [8, 9]. Other forms of RNA, including transport, ribosomal, small nucleolar, short and long noncoding RNAs, have also been identified in

exosomes [10]. They can be transferred from host cells to recipient cells to regulate cellular functions [11].

As mentioned above, exosomes include microRNAs, small noncoding RNA molecules 18 to 25 nucleotides long [2,7], which regulate the work of about 60% of the genes encoding proteins in the cell. It turned out that miRNAs are unusually widespread in exosomes, at least more than 600 different types of microRNA are found in their composition [12]. These microRNAs are secreted by a variety of cells: immune system cells, blood cells, stem cells and many other cells, and they control many cellular processes such as proliferation, differentiation, and cell death. All of them secrete exosomes with different microRNA content, corresponding to the physiological tasks of specific exosomes [7]. It was found that miRNAs modulate gene expression at the post-transcriptional level by binding to the 3'-noncoding regions of their mRNA targets [13].

To date, a large amount of evidence has been accumulated on the involvement of exosome miRNAs in the carcinogenesis of various malignant neoplasias, including lung cancer, which is the main cause of death from malignant neoplasms worldwide [14,15,16]. Although the risk and incidence of lung cancer are slightly higher among men, this cancer is becoming the leading cause of cancer death among women as well. Lung cancer is very difficult to diagnose in the early stages of the tumor process, which makes the treatment of this disease loweffective. In this regard, early detection of the disease through the use of new biomarkers is a promising strategy for reducing mortality from lung cancer. An important method for the diagnosis of tumors is a liquid biopsy from samples of blood serum and plasma, which can be used to obtain a complete molecular profile of genomic changes that occur in several areas of primary tumors in real time [17, 18]. During carcinogenesis, tumor cells constantly interact with each other and with normal host cells to accelerate cell growth and survival. Exosomes derived from tumor cells are involved in these communication processes by transferring their various ingredients from donor to recipient cells [19].

The development of non-invasive methods for the study of exosomes containing microRNAs of tumor cells for early diagnosis and monitoring of tumor growth is today an actual problem of oncology. In this regard, exosome miRNAs are currently actively used as molecular biomarkers for the diagnosis of lung cancer [16, 18]. When comparing the expression of exosomal miRNA in patients with non-small cell lung cancer and healthy people, more than thirty miRNAs were found, which showed differential expression [20].

Structure and function of exosomes

Exosomes are extracellular membrane vesicles, 30–100 nm in diameter, of endocytic origin, which are formed during the formation of a multivesicular body and are secreted into the extracellular space [21, 22]. Exosomes are the result of four sequential processes occurring in the cell - initiation, endocytosis, formation of the multivesicular body and secretion [1,22].

The process of exosome formation begins with invagination of microdomains of the cytoplasmic membrane with the formation of an early endosome. The early endosome matures into a late endosome, which then transforms into a multivesicular body, which can attach to the plasma membrane from the inside and release exosomes into the extracellular space [1,2].

Microvesicular particles secreted by cells are divided into two classes that differ in the mechanism of secretion: 1) microvesicles formed directly from the plasma membrane and have an average larger size (100-1000 nm), and 2) exosomes secreted from cells by fusion with the plasma membrane microvesicular particles (combined into one concept with late endosomes), which include future exosomes, also called intraluminal vesicles [23,24]. Thus, it is obvious that the mechanism of exosome secretion is the result of vesicular transport and is directly related to endocytosis [22,23,25]. The internal contents, size and membrane composition of extracellular vesicles are always heterogeneous and

depend on the type of donor cell, its functional state and environmental conditions [23].

After their discovery, the main function of exosomes was considered to be the rapid removal of some proteins from cells, mainly membrane bound [6]. However, it was later found that exosomes can transport various biomolecules to recipient cells, including proteins, RNA, DNA, microRNA, viral particles, causing a whole range of changes in cells at the genomic and epigenomic levels [2,4]. Exosomes are secreted by almost all cells in the body and carry a variety of signals to recipient cells. The mechanism of interaction of exosomes with recipient cells is not fully understood. Several variants of such a mechanism are being considered, including: 1) ligand-receptor interactions; 2) embedding of the exosomal membrane into the cell membrane; 3) phagocytosis of exosomes by recipient cells [24]. It has been shown that exosomes obtained from infected cells contain pathogenic antigens that modulate the immune response. In particular, exosomes of endothelial cells infected with cytomegalovirus are capable of inducing a specific immune response [4]. It has been shown, for example, that exosomes of macrophages infected with human immunodeficiency virus of the first type bind specifically to T-cells, which ensures the spread of infection and suppression of the immune response [26]. Exosomes of different subpopulations of T- cells contain different miRNAs [27].

The content of certain types of RNA may vary depending on the source of the exosome. The first experimental evidence that exosomes can carry mRNA were studies by Ratajczak et al. [28], who showed that when processing mouse mononuclear bone marrow cells with exosomes from embryonic stem cells, in the cytoplasm of which there is a lot of mRNA of the transcription factor of the Ost4 protein, hematopoietic cells are reprogrammed and an increased synthesis of this protein occurs. Later, it was shown that the transfer of mRNA and microRNA by exosomes to target cells promotes tissue regeneration after exposure to stress [29].

As mentioned earlier, exosomes also contain mitochondrial DNA, single-stranded and double-stranded DNA [8,9]. The exosomal composition of DNA has been much less studied than the composition of RNA. The presence of DNA in exosomes usually indicates pathological conditions such as cancer, genetic disorders, etc. [30].

The role of exosomes in carcinogenesis

Exosomes play an important role in the development of pathological conditions. Exosomes of bronchial epithelial cells, containing an increased amount of cytokines, in the case of bronchial asthma, provide the spread of the anti-inflammatory effect in all tissues of the respiratory system [31]. It has been shown that tumor cells produce exosomes in much larger quantities than normal cells. Exosomes produced by tumor cells are found in almost all body fluids, including blood serum, urine, semen, ascites and pleural fluids. Due to the presence on their membranes of adhesion receptors and ligands specific for various types of cells and tissues, exosomes interact with certain types of cells, delivering biological molecules of the widest spectrum of action to the latter, including growth factors, cytokines, receptors, bioactive lipids and various types of RNA [22,23,26].

The secretion of exosomes has been shown for the vast majority of malignant tumors, and this process is a characteristic feature of neoplastic cell transformation [32].

Exosomes originating from tumor cells play a role in the communication of tumor cells through the transfer of their various ingredients from donor to recipient cells [33] and affect both their microenvironment and distant organs, where they can promote angiogenesis, proliferation and metastasis. Exosomes, which are significantly involved in cancer growth and metastatic spread, are considered the main cause of paracrine effects on recipient cells. Regulation of oncogene expression and abnormal transformations can also result from various effects of initiation factors. Eukaryotic translation initiation factor 3 (elF3) binds the 43S preinitiation complex and elF4F-bound mRNA to control protein synthesis, and their aberrantly expressed subunits are associated with various types of cancer [34, 35].

Exosomes create a complex network of interactions that suppress the immune system, delivering the contents of tumor cells to immune cells, as well as disrupt the activation of natural killer cells and induce apoptosis of effector T-cells [36]. Exosomes can not only form an immunoprivileged environment within the tumor tissue, but also transfer proapoptotic molecules, for example, Fas ligand molecules, which cause the death of activated antitumor T- lymphocytes [37, 38]. It was shown that tumor endosomes suppress lymphocyte differentiation by modulating the expression of interleukin-2 [39]. Tumor exosomes not only increase the number and activity of immunosuppressive cells, but also promote the active transfer of various viruses, including viruses associated with carcinogenesis. There is evidence that exosomes mediate cell resistance to radiation by interacting with the cell cycle and DNA repair processes [40].

As mentioned above to date, a large body of evidence has been accumulated on the involvement of microRNAs in the carcinogenesis of various malignant neoplasias. MiRNAs are key regulators of gene expression in cancer, functioning as either tumorsuppressors or oncogenes depending on the target mRNA, and play a important role in tumorigenesis. Exosomes provide highly stable source of miRNAs in body fluids, protecting them against degradation even under nonphysiological conditions. It was shown that exosomal microRNAs remain stable during longterm storage at room temperature [42]. Their enhanced stability compared to proteins and other nucleic acids, both in the circulation and in fixed tissues, makes exosomal microRNAs well-suited to analysis. MiRNAs are taken up by nearby or distal target recipient cells as a cargo of exosomes, reflecting a cell-to-cell communication method that can influence the pathogenesis of cancer. Cazzoli et al. found two sets of exosome miRNAs,which not only allowed them to distinguish lung nodule patients from healthy former smokers,but also to distinguish lung adenocarcinoma and granuloma [43].

In tumor cells, microRNA-regulated genes for apoptosis, cell division, and differentiation determine the nature of the tumor. It has been shown that exosomal miRNAs are involved in regulatory processes in diseases of various systems, including cardiovascular [44], neurological [45], and urinary tract diseases [46], especially malignant tumors [47] in these systems.

The set of microRNAs and their ratio in exosomes of cells, blood plasma and other biological fluids in colon cancer [48], ovary [49], and pancreas [50] were determined. It was shown that the set of miRs and their ratio in exosomes in the serum (plasma) of blood corresponds to that in exosomes of tumor cells in the same patient. It was demonstrated, that cancer cell released exomiR-21, exomiR-23, exomiR-29, exomiR-103, and exomiR-210 promote tumor proliferation, angiogenesis, and migration [51]. In particular, exo-miR-21 may be a promising biomarker for many types of cancer [47]. In many tumors, there is an increased content of let7 miR, which regulates the Ras protein, miR-15, miR-16, and regulates the activity of mRNA Bcl-2, miR-21, miR-214 [13, 16]. It has been shown that tumor microRNAs isolated from exosomes can be successfully used for the early diagnosis of prostate cancer, bladder cancer, colorectal cancer, brain tumors, and pancreatic cancer [45,48,52].

Role of exosomal microRNA in diagnosis of lung cancer

Recent studies have shown that exosomal miRNAs play an important role in the pathogenesis and progression of several lung diseases, including lung cancer, chronic obstructive pulmonary disease, asthma, tuberculosis, and interstitial lung disease [18,53,54]. However, the expression patterns of miRNAs differ depending on physiological and pathological conditions, which may mean that these exosomal biomolecules have the potential to ward off disease states. In addition, it has been shown that the profiles of exosomal miRNA in patients with lung disease differ from those in healthy people. The analysis of exosome contents allows for differential diagnosis of benign and malignant lung tumors. Exosomal miRNAs are likely to become non-invasive diagnostic biomarkers of lung diseases, including lung cancer.

Several studies addressed circulating miRNA as potential molecular signatures to be used for the diagnosis of lung cancer. Numerous papers have been published in last decade that described signatures of serum/plasma miRNA, which enabled the differentiation between lung cancer patients and healthy individuals [18,53,54,55]. Most of these reports described multi-component miRNA [55]. To identify the miRNAs in exosomes that participate in the lung cancer many studies have measured exosomal miRNA profiles in blood plasma and serum. The results of these studies recently were summarized by Smolarz and Widlak [55]. Proposed lung cancer signatures involved more than 100 miRNA species overall, which included 39 miRNA species that recurred in more than one signature. It was shown that four miRNA species were included in more than five signatures, namely, miR-21 (11 signatures), miR-148b (8 signatures), miR-126, and miR-486–5p (seven signatures) [55].

Circulating miRNA profiles are different for each cancer microenvironment and stage of tumor progression. The microRNA profile can change due to exposure to both chemical and physical environmental factors [56,57]. The comparison between microRNAs in the patients with non-small cells lung cancer (NSCLC), and the healthy controls showed that the plasma miR-18a and miR-126 expression levels were lower in the patients with NSCLC, whereas the expression levels of miR-19a, miR-20a, miR-92a, miR-130a, miR-210, miR-296, and miR-378 were higher in the patients with NSCLC [54].

Several studies have shown that the epigenetic basis of lung cancer is associated with changes in the miRNA's expression profile [56,57]. Epigenetic changes primarily allowing the cell to adapt to environmental factors. Currently, the problem of radon exposure to the human is widely studied worldwide. In Kazakhstan, this problem remains poorly understood, despite the fact that most of the territories of the Republic of Kazakhstan are classified as radon-hazardous. For the moment, the association of radon and the risk of lung cancer is not in doubt, but the mechanism of how radon induces malignant cell transformation remains unclear. Most of the existing research in the current literature concerns the genetic aspects of the etiology and pathogenesis of radon-induced lung cancer [57]. We examined 136 subjects, including 49 patients with lung cancer exposed to radon, 37 patients with lung cancer without radon exposure, and 50 volunteers as a control group. The level of free-circulating microRNA hsa-miR-19b-3p was significantly higher in groups of patients with lung cancer compared with healthy individuals. Our results indicate that the detection of hsa-miR-19b-3p levels in blood plasma can potentially be used as a non-invasive method for diagnosing lung cancer [58] and further identification of miRNAs as a specific marker of radon exposure becomes very relevant. However, a major disadvantage of this approach is the low specificity of the method based on free-circulating miRNAs and the inability to obtain miRNAsdirectly from tumor tissue. Therefore, the study of the exosomal miRNAsis the most informative method. Exosomes contain proteins and genetic material (including microRNAs) derived from their parent cells, and can potentially affect recipient cell sand cargos in exosomes can be used as potential diagnostic and prognostic cancer biomarkers [2,6,7]. However, evidence on the relationship of exosomes and exosomal miRNAs with radon are currently unavailable. Therefore the study of radon-mediated changes in the exosomal miRNAsfrom bronchial epithelial cells and its influence on such processes as inflammation, cytokine production, and induction of cell death is very relevant. Taking into account the situation with radon risk and the incidence of lung cancer in Kazakhstan, the search for markers that can detect early radon-induced changes that lead to malignant transformation of bronchial epithelial cells is very relevant. In summary, lung cancer is the most common form of malignant neoplasia and is one of the leading causes of cancer death. Early detection of lung cancer is screening programs is a rational way to reduce mortality from this disease. Many studies have reported the functions of exosomes and exosomal miRNAs in different types of cancer, including lung cancer. Exosomal miRNA mediate cell-to cell communication, which participates

in the development of lung cancer. In this review was analysed recent knowledge about the roles of exosomes and possibility of using exosomal miRNAs as biomarker in early detection of lung cancer.

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Өкпенің қатерлі ісігін диагностикалаудағы экзосомалар мен экзосомалық микроРНҚ рөлі

Аңдатпа. Экзосомалар - бұл жасушадан жасушаға ақпарат тасымалдаушысы ретінде қызмет ете алатын, жасушааралық байланыста плеотропты функцияларды қамтамасыз ететін жасушалардың барлық дерлік түрлері шығаратын жасушадан тыс везикулалар. Экзосомалар қабылдаушы жасушаларға әртүрлі биомолекулаларды, соның ішінде ақуыздар мен нуклеин қышқылдарын тасымалдай алады. Әдеби шолуда экзосомалардың рөлі және өкпе қатерлі ісігін диагностикалауда биомаркер ретінде экзосомалық микроРНҚ қолдану мүмкіндігі туралы заманауи мәліметтер қарастырылған. МикроРНҚ онкогендер немесе ісік супрессорлары ретінде әрекет ете алады, сондықтан олар онкогенезде маңызды рөл атқаратын гендердің экспрессиясын реттей алады. Қазіргі уақытта экзосомалық микроРНҚ қатерлі ісік диагнозын қою үшін сұйық биопсияның молекулалық маркерлерінің рөліне негізгі кандидаттардың бірі болып табылады. Әдеби шолу экзосомалық микроРНҚ-ны өкпе қатерлі ісігінің биомаркері ретінде қолдануға баса назар аудара отырып, канцерогенезде экзосомаларды қолданудың диагностикалық әлеуеті талданды.

Түйін сөздер: өкпенің қатерлі ісігі, экзосома, экзомалық микроРНҚ, диагностика, сұйық биопсия.

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Экзосомы и роль экзосомальной микроРНК в диагностике рака легкого

Аннотация. Экзосомы представляют собой внеклеточные везикулы, выделяемые почти всеми типами клеток, которые могут функционировать в качестве переносчика информации от клетки к клетке, обеспечивая плейотропные функции в межклеточной коммуникации. Экзосомы могут транспортировать в клетки-реципиенты различные биомолекулы, в том числе белки и нуклеиновые кислоты. В обзоре рассмотрены современные данные о роли экзосом и возможности использования экзосомальных микроРНК в качестве биомаркера при диагностике рака легкого. МикроРНК могут действовать как онкогены или как супрессоры опухолей, поэтому они могут регулировать экспрессию генов, которые играют важную роль в онкогенезе. На данный

момент микроРНК экзосом являются одними из основных кандидатов на роль молекулярных маркеров жидкой биопсии для диагностики онкологических заболеваний. В обзоре проанализирован диагностический потенциал использования экзосом в канцерогенезе в целом, с акцентом на использование экзосомальных микроРНК в качестве биомаркеров рака легких.

Ключевые слова: рак легких, экзосомы, экзосомальная микроРНК, диагностика, жидкостная биопсия.

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