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miRNA and cell free-circulated mitochondrial DNA as potential biomarkers of lung cancer

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Lung cancer is the most common form of malignant neoplasia. According to the Institute of Oncology and Radiology, lung cancer in the Republic of Kazakhstan ranks second and accounts for 11.1% of all cases in the structure of oncological diseases. The search for biomarkers that can become highly sensitive and specific molecular markers for the early diagnosis of this pathology remains in great demand. Lung cancer is a multifactorial disease based not only on genetic factors, but also on environmental factors. The International Agency for Research on Cancer has identified exposure to radon and asbestos as major carcinogenic risk factors for lung cancer. It has been shown that radon can induce specific genetic and epigenetic changes in lung tissue, leading to aberrant function of oncogenes and tumor suppressor genes.

In recent years, in the laboratory of molecular genetics of the Institute of Cell Biology and Biotechnology of L.N. Gumilyov Eurasian National University, research has been actively carried out to study the role of miRNA and free-circulating mitochondrial DNA (cf-mitDNA) as biomarkers for non-invasive diagnosis of lung cancer.

The epigenetic basis of lung cancer is primarily associated with changes in miRNAs profiles. We examined the expression level of miR-19b-3p and hsa-miR-125b-5p in patients diagnosed with lung cancer. Overexpression of miR-19b-3p was revealed in malignant lung tumors. The expression profile was also significantly changed of the exosomal fraction hsa-miR-125b-5p and hsa-miR-320c in the blood plasma of people exposed to high doses of radon. In addition, a dose-dependent effect of radon on the expression of these miRNAs was found. On the lung fibroblast cell line MRC5, a change in the expression profile of 6 types of microRNAs under the influence of chrysotile asbestos was shown: hsa-miR-19b-3p, hsa-miR-125b-5p, hsa-miR-181b-5p, hsa-miR-376b-3p, hsa-miR-1202 and hsa-miR-122.

Our studies have demonstrated that cf-mtDNA may be another promising biomarker of changes in lung tissue under the influence of carcinogenic factors. In individuals living in areas with elevated radon levels, this indicator was significantly higher not only in comparison with the control group, but also in comparison with patients with lung cancer not caused by radon. It has also been shown to be a sensitive and specific biomarker for radon-induced lung cancer.

One of the main damaging mechanisms of asbestos is the induction of oxidative cellular stress and its genotoxic effect due to an increase in ROS content. The result is damage to cellular components and DNA. We found a dose-dependent increase in ROS level in a MRC5 cell line exposed to asbestos. Chrysotile asbestos shows a dose- and time-dependent cytotoxic effect on lung fibroblasts. Lung cancer's molecular basis involves accumulating genetic and epigenetic changes, weakening DNA structure and increasing mutation susceptibility. Exposure to both radon and asbestos has been shown to increase the levels of pro-inflammatory cytokines. Our studies suggest that radon and asbestos alter miRNAs expression, leading to bronchial epithelial cell death and the release of cf-mtDNA. This activates the NF-κB pathway, triggering inflammation, a key factor in oncogenesis. Mitochondria play a central role in malignant transformation, including lung cancer. These findings highlight the potential of miRNAs and cf-mtDNA as biomarkers for non-invasive lung cancer diagnosis, disease prognosis, and indicators of environmental risk factors for lung malignancies.