IRSTI 34.15.51

Zumama Khalid

University of Genova, Department of Health Science, Genoa, Italy
E-mail: zumama.khalid@gmail.com

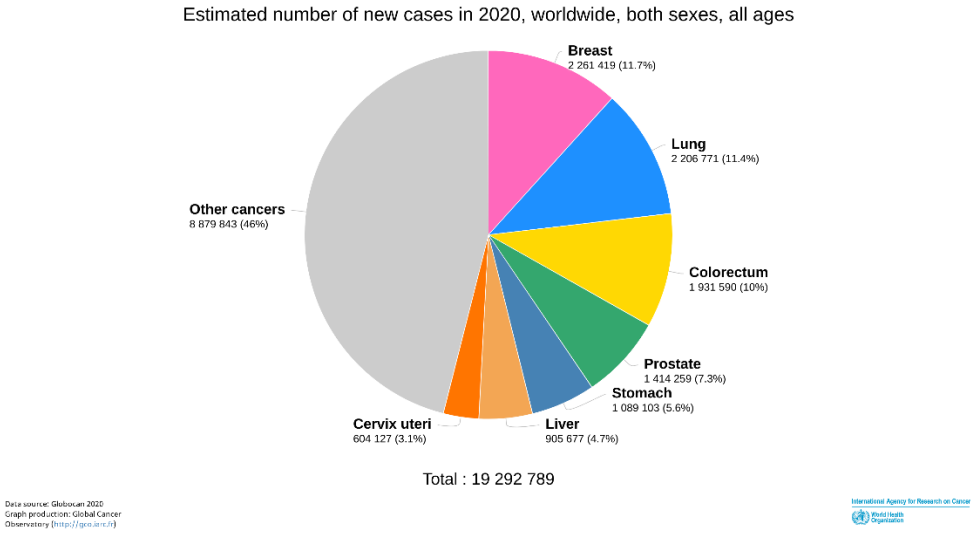
Circular RNA as a novel molecular biomarker for radon-induced lung cancer

Abstract. *Circular (circ) RNAs are non-coding closed RNA molecules. Studies of human tumors, including lung cancer, have shown a change in the expression profile of circrna. CircRNA can indirectly regulate gene expression by binding and inhibiting microRNA functions. Thanks to this mechanism, circRNAs can regulate proliferation, apoptosis, invasion, and metastasis. In this review, we showed a brief description of the expression and function of circRNAs, as well as their roles in the development of lung cancer. We presented evidence that these molecules should be studied as useful biomarkers for radon-induced lung cancer.*
Keywords: *circRNAs, microRNA, lung cancer, biomarkers, radon.*

DOI: 10.32523/2616-7034-2021-137-4-113-123

The problem of lung cancer

The World Health Organization annually lists lung cancer among the leading causes of death. Mortality from this disease is growing rapidly. In 2019, lung cancer ranked 6th in the number of deaths among other diseases (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). According to the data (https://gco.iarc.fr /) in 2020, lung cancer was one of the most common forms of oncology (11.4%) and breast cancer (11.7%) was the second one.



The prevalence and mortality from lung cancer are increasing every year. Statistics show that only 26% and 8% of cancer cases are diagnosed at stages I and II, while 28% and 38% are diagnosed at stages III and IV, respectively [1].

Today, the main causes of detecting tumors in the lungs are methods of radiation (fluorography and X-ray) and X-ray diagnostics (CT and MRI). It is worth noting, however, that in both cases, patients are referred for research after the onset of symptoms. Non-small cell lung cancer is a rather aggressive form of lung tumor, which is reflected in the short progression time of the disease [2]. Therefore, by the time the first symptoms appear, lung cancer is often already in an advanced stage. In this regard, it is necessary to find new ways of early diagnosis and detection of the risks of lung cancer in the framework of screening the population. The introduction of screening for lung cancer will lead to the possibility of

early diagnosis, as well as the identification of the risks of developing tumors.

Many studies have already shown the relationship between lung cancer and various molecular markers: genetic polymorphisms [3, 4], freely circulating nucleic acids [5, 6], and microRNA molecules [7, 8].

Lung cancer risk factors

It should be noted that lung cancer is primarily a multifactorial disease. This means that lung cancer has several risk factors, which are a combination of genetic and environmental factors. [9]. A high correlation has been demonstrated between smoking and lung cancer. Tobacco smoke has a complex composition containing more than 5000 substances, some of which are recognized as carcinogenic. These compounds can damage various cellular structures, provoking the cell to malignant transformation [10]. However, smoking is just an external factor. The hydrophobic condensate of cigarettes (HCC) can influence various cellular proteins and molecules. The effect of HCC on the RBM5 protein, which is a cell cycle modulator, is known. Overexpression of RBM5 attenuates cell proliferation and invasion and reduces invasion mediators such as hypoxia-induced (HIF-1α), VEGF, and matrix metalloproteinase (MMP-2). It has been shown to suppress RBM5 in lung cancer [11]. It was also found that changes in the cell cycle are associated with the suppression of miR-218. HCC causes a decrease in miR-218 levels and, consequently, an increase in the level of the CCAT1 protein in human bronchial epithelium (HBE) cells. This contributes to the active proliferation, migration, and invasion of the tumor cells [12]. Although cigarette smoke is recognized as the leading cause of lung tumors, it is known that approximately 10% of all lung cancer cases in the United States were diagnosed in never-smoked patients [13]. Other factors that provoke the onset and progression of this disease are officially recognized as radon and asbestos [14].

Radon is a radioactive inert gas that makes up the natural radiation background of our planet. It is formed during the decay of uranium in the soil. In the future, it will penetrate the residential premises through cracks in the foundation, where it can accumulate for a long time [15]. According to statistics, radon exposure is associated with more than 20,000 deaths from lung cancer per year in the United States [16]. WHO has established maximum permissible levels for most countries of 100 Bq/m3, (https://www.who.int/ru/news-room/fact-sheets/detail/radon-and-health) however, in some countries this value has been increased to 200 Bq/m3. However, Lorenzo-Gonzalez et al. has shown that radon is a serious risk factor for lung cancer in non-smoking patients exposed to radon above 200 Bq/m3 [17].

Radon is a risk factor for lung cancer

With respiration, radon enters directly into the lungs, which are the main target of its effects. Radon isotopes are not stable and continue to decay into other elements. Each such transformation is accompanied by the generation of α and β particles. These particles pass through the cells, irradiate them with ionizing radiation. This leads to the oxidation of cellular components and DNA (double-strand breaks in DNA, chromosomal aberrations) [18].

Seven point mutations and two deletions of the TP53 tumor suppressor gene were found in the study of radon-induced lung cancer in uranium mine workers [19]. Although this study is more likely about the cumulative effects of ionizing radiation from radon and smoking. However, world statistics show that in countries where the uranium mining industry is developed, it is lung cancer that occupies a leading position among other oncological diseases. According to the International Agency for Research on Cancer, in 2020, 12% of all cases in Kazakhstan were lung tumors, in Canada (11.5%), Australia (7.2%), USA (11.7%), Germany (11%) and Spain (11.05%) (http://gco.iarc.fr).

However, uranium miners are not alone at risk of radon-induced lung risk. A pooled meta-analysis of the study showed that 6.9% of lung cancer cases in Canada were associated with home exposure to radon [20].

It is known not only about the association of radon with the risk of developing lung cancer among the population. The dependence of the risk on the exposure dose is also noted. Torres-Duran et al. determined that people who were exposed to more than 200 Bq/m3 of radon had a higher risk of lung cancer than those who were exposed to low (<100 Bq/m3) [21]. Moreover, a concentration of up to 1 is known to increase the risk of lung cancer by 7% annually [22].

There is not much data that reveals the molecular aspects of the carcinogenic effect of radon. A study of microRNA profiles in lung epithelial cells exposed to radon radiation was performed. Profiling showed changes in the expression of many microRNAs, including those involved in the transformation of malignant transformation of cells [23]. According to Wu J. et al., overexpression of miR-34a was found during prolonged exposure to radon, which in turn increased the expression of the pro-apoptotic protein Bax, as a result, it enhances cell apoptosis [24].

Irradiation with high doses of radon contributes to the migration and proliferation of epithelial cells, a decrease in cell adhesion due to a decrease in epithelial markers, and an increase in mesenchymal markers. Radon regulated the expression of matrix metalloproteinase 2 (MMP2) and tissue inhibitors of metalloproteinase 2 (TIMP2). Moreover, exposure to radon leads to an increase in p-PI3K, p-AKT, and p-mTOR, which induces cell invasion [25].

Exposure to radon causes aseptic inflammation in the tissues. It was shown that the level of cf mtDNA in patients with radon-induced lung cancer was significantly higher than in patients who were not exposed to high doses of radon and healthy donors [26].

Thus, there is no doubt about the relationship between radon exposure to the human body and the risk of lung cancer. However, the molecular mechanisms of carcinogenesis require further study.

Circular RNA, biogenesis, and basic functions

Circular RNA (circRNA) is a class of non-coding, covalently closed RNA molecules. In multicellular organisms, the expression of circular RNA is tissue specific. Due to the absence of free 3'- and 5'-ends, circRNAs are practically do not subject to cleavage by nucleases, which makes them more stable than most linear RNAs [27]. To date, many circRNAs have been identified and their role in the development and progression of oncology is known [28, 29].

circRNAs, like linear RNAs, are transcribed by RNA polymerase II (Pol II) and contain introns and exons. Their further splicing takes place using a special type of splicing called "reverse splicing". With this type of splicing, the 5'-end of the molecule is 3'-end, which leads to a 3'-5 'phosphodiester bond, which forms a circular RNA molecule [30].

Mature CircRNAs are usually located in the cytoplasm. The mechanisms of their nuclear export have not yet been fully elucidated; their translocation most likely occurs with the help of RNA-binding proteins [31].

CircRNAs can function as a sponge for microRNA molecules (miRNAs), which inhibit miRNA activity and regulate the expression of their target genes [32].

Wei et al. found an increase in circZFR in thyroid cancer compared to adjacent normal tissues. CircZFR promotes the expression of C8orf4, acting as a trap for miR-126. Thus, circZFR promotes proliferation, migration, and invasion of thyroid cancer cells [33]. Another circRNA; circNEURL4 can bind to miR-1278 and, thus, indirectly regulate the expression of LATS1 and, probably, can serve as a diagnostic marker of thyroid cancer [34]. hsa_circ_0000977 can regulate the expression of the PLK1 gene by inhibiting hsa-miR-874-3p in pancreatic adenocarcinoma [35].

The role of circRNAs in the development of lung cancer

Studies have shown that circRNA can indirectly regulate the expression of proteins associated with the risk of lung cancer. There is a high level of CDR1as expression in NSCLC tissues. Overexpression of CDR1as functions as an inhibitor of miR-7, increasing the expression of miR-7 target

genes, including EGFR, CCNE1, and PIK3CD. In vivo results further confirmed that CDR1as function as an oncogene in lung cancer [36].

Overexpression of circMAN2B2 in lung cancer was detected. circMAN2B2 regulates FOXK1 expression through miR-1275 binding, which increases the proliferation and invasion of lung cancer cells H1299 and A549 [37].

Wang et al. found that the localization of hsa_circ_0012673 in the cytoplasm promotes the proliferation of lung adenocarcinoma cells by inhibiting miR-22, which targets tyrosine kinase 3 of the erb-b2 receptor (ErbB3) [38].

High expression of hsa_circ_0020123 was observed in NSCLC tumor tissues, which was associated with poor survival prognosis and lymph node metastases. miR-144 has been identified as a target for hsa_circ_0020123. By binding to miR-144, hsa_circ_0020123 can activate ZEB1 and EZH2. While the hsa_circ_0020123 knockdown significantly inhibits the proliferation and invasion of adenocarcinoma cells and delays tumor growth in vivo [39].

circRNA-FOXO3 is a tumor suppressor in NSCLC and may serve as a promising therapeutic target. circRNA-FOXO3 inhibits tumor growth role by binding to miR-155 and indirectly regulating the expression of FOXO3. Dysregulation of FOXO3 is associated with the development of cancer due to the regulation of increased AKT activity or PTEN inactivation, therefore FOXO3 is classified as a tumor suppressor [40].

Hsa_circ_0000064 can act as a promising biomarker and therapeutic target for lung adenocarcinoma. With metastasis, there is a noticeable increase in hsa_circ_0000064. The hsa_circ_0000064 knockdown suppressed cell proliferation, promotes apoptosis, and blocks the cell cycle in cells A549 and H1229, which may be associated with reduced expression of MMP-2 and MMP-9 [41].

Circ_0016760 was highly expressed in NSCLC, which is associated with rapid tumor development and an unfavorable prognosis in patients. circ_0016760 can be considered as a predictive biomarker for NSCLC. Mechanically, circ_0016760 acts as a sponge for miR-1287 and regulates the expression of GAGE1. Thus, circ_0016760 can participate in NSCLC oncogenesis by transmitting circ_0016760 / miR-1287 / GAGE1 signals [42].

Liu et al. found that the expression of circ-FOXM1 was closely associated with tumor invasion from lymph nodes and an unfavorable prognosis for patients with NSCLC. Circ-FOXM1 promoted proliferation and invasion of NSCLC cells by regulating PPDPF and MACC1 levels through the regulation of miR-1304-5p. This indicates that circ-FOXM1/miR-1304-5p/PPDPF/MACC1 signaling is an important element for the development and progression of NSCLC [43].

Conclusion

Numerous studies have shown that altered circRNA expression may affect carcinogenesis and lung cancer progression. circRNAs are clinically important as they can be used as diagnostic markers and therapeutic targets. circRNAs have several advantages. These molecules remain relatively stable structures, suggesting that circular RNAs are ideal diagnostic biomarkers for the early diagnosis of lung cancer. Based on the functional activity of circRNAs and communication with microRNA molecules, complete diagnostic panels can be developed. Moreover, there are already data on the changes in the circRNAs profiles upon exposure to radon [44] and radiation exposure [45]. These studies provide a basis for the study of circRNAs as molecular markers for radon-induced lung cancer.

References

1. Siddiqui F., Siddiqui A.H. Lung Cancer. [Updated 2021 Sep 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls.

2. Reck M., Kerr K.M., Grohé C., Manegold C., Pavlakis N., Paz-Ares L., Huber R.M., Popat S., Thatcher N., Park K., Hilberg F., Barrueco J., Kaiser R. Defining aggressive or early progressing nononcogene-addicted non-small-cell lung cancer: a separate disease entity? Future Oncol. -2019. -Vol. 15(12). P. 1363-1383.

3. Chang J.H., Lai T.C., Yang P.J. et al. Associations of TIMP-3 Genetic Polymorphisms with EGFR Statuses and Cancer Clinicopathologic Development in Lung Adenocarcinoma Patients. Int J Mol Sci. 2020;21(21):8023., Xu, Shuguang MDa,b; Ying, Kejing MDa, Association between HIF-1α gene polymorphisms and lung cancer, Medicine: June 12. -2020. -Vol. 99, Issue 24. -P. e20610.

4. Sengupta D., Banerjee S., Mukhopadhyay P. et al. A comprehensive meta-analysis and a case-control study give insights into genetic susceptibility of lung cancer and subgroups. Sci Rep. -2021. -Vol.11. -P. 14572.

5. Pasquale R., Forgione L., Roma C., Fenizia F, Bergantino F., Rachiglio A.M., De Luca A., Gallo M., Maiello M.R., Palumbo G., Morabito A., Azzaro R., Normanno N. Targeted sequencing analysis of cell-free DNA from metastatic non-small-cell lung cancer patients: clinical and biological implications. Transl Lung Cancer Res. -2020. -Vol.9(1). -P. 61-70.

6. Gou Q., Zhang C.Z., Sun Z.H., Wu L.G., Chen Y., Mo Z.Q., Mai Q.C., He J., Zhou Z.X., Shi F., Cui W., Zou W., Lv L., Zhuang W.H., Xu R.D., Li W.K., Zhang J., Du H.W., Xiang J.X., Wang H.Z., Hou T., Li S.T., Li Y., Chen X.M., Zhou Z.J. Cell-free DNA from bile outperformed plasma as a potential alternative to tissue biopsy in biliary tract cancer. ESMO Open. -2021. -Vol.12;6(6), -P.100275.

7. Duan X., Qiao S., Li D., Li S., Zheng Z., Wang Q., Zhu X. Circulating miRNAs in Serum as Biomarkers for Early Diagnosis of Non-small Cell Lung Cancer. Front Genet. -2021. -Vol. 9(12). -P.673926.

8. Dama E., Colangelo T., Fina E., Cremonesi M., Kallikourdis M., Veronesi G., Bianchi F. Biomarkers and Lung Cancer Early Detection: State of the Art. Cancers (Basel). -2021. -Vol.3;13(15). -P. 3919.

9. Shankar A., Dubey A., Saini D. et al. Environmental and occupational determinants of lung cancer. Transl Lung Cancer Res. -2019. -8(Suppl 1). -P. S31-S49.

10. Dela Cruz C.S., Tanoue L.T., & Matthay R.A. Lung cancer: epidemiology, etiology, and prevention. Clinics in chest medicine. -2011. -Vol.32(4). -P.605–644.

11. Bechara E.G., Sebestyén E., Bernardis I., Eyras E., Valcárcel J. RBM5, 6, and 10 differentially regulate NUMB alternative splicing to control cancer cell proliferation. Molecular cell. -2013. -Vol. 52(5). -P. 720–733.

12. Lu L., Xu H., Luo F., Liu X., Lu X., Yang Q., Xue J., Chen C., Shi L., Liu Q. Epigenetic silencing of miR-218 by the lncRNA CCAT1, acting via BMI1, promotes an altered cell cycle transition in the malignant transformation of HBE cells induced by cigarette smoke extract. Toxicology and applied pharmacology. -2016. -Vol. 304. -P. 30–41.

13. Rivera G.A., Wakelee H. Lung Cancer in Never Smokers. Advances in experimental medicine and biology. -2016. -Vol.893. -P.43–57.

14. Hubaux R., Becker-Santos D.D., Enfield K.S., Lam S., Lam W.L., Martinez V.D. Arsenic, asbestos, and radon: emerging players in lung tumorigenesis. Environ Health. -2012;11:89.

15. Azara A., Dettori M., Castiglia P., Piana A., Durando P., Parodi V., Salis G., Saderi L., Sotgiu G. Indoor Radon Exposure in Italian Schools. International journal of environmental research and public health. -2018. -Vol.15(4). -p. 749.

16. U.S. Environmental Protection Agency. Radon health risks. Washington D.C.: U.S. Environmental Protection Agency. -2012.

17. Lorenzo-González M., Ruano-Ravina A., Torres-Durán M., Kelsey K.T., Provencio M., Parente-Lamelas I., Leiro-Fernández V., Vidal-García I., Castro-Añón O., Martínez C., Golpe-Gómez A.,

Zapata-Cachafeiro M., Piñeiro-Lamas M., Pérez-Ríos M., Abal-Arca J., Montero-Martínez C., Fernández-Villar A., & Barros-Dios J.M. Lung cancer and residential radon in never-smokers: A pooling study in the Northwest of Spain. Environmental research. -2019. -Vol. 172. -P.713–718.

18. Hubaux R., Becker-Santos D.D., Enfield K.S., Lam S., Lam W.L., Martinez V.D. Arsenic, asbestos, and radon: emerging players in lung tumorigenesis. Environ Health. -2012;11:89.

19. Vähäkangas K.H., Samet J.M., Metcalf R.A., Welsh J.A., Bennett W.P., Lane D.P. & Harris C.C. Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. Lancet (London, England). -1992. -Vol. 339(8793). -P. 576–580.

20. Gogna P., Narain T.A., O'Sullivan D.E., Villeneuve P.J., Demers P.A., Hystad P., Brenner D.R., Friedenreich C.M., King W.D. & ComPARe Study Team. Estimates of the current and future burden of lung cancer attributable to residential radon exposure in Canada. Preventive medicine. -2019. -Vol. 122. -P. 100–108.

21. Torres-Durán M., Ruano-Ravina A., Parente-Lamelas I., Leiro-Fernández V., Abal-Arca J., Montero-Martínez C., Pena-Álvarez C., González-Barcala F.J., Castro-Añón O., Golpe-Gómez A., Martínez C., Mejuto-Martí M.J., Fernández-Villar A. & Barros-Dios J.M. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). The European respiratory journal. -2014. -Vol. 44(4). -P.994–1001.

22. Zhang Z.L., Sun J., Dong J.Y., Tian H.L., Xue L., Qin L.Q., Tong J. Residential radon and lung cancer risk: an updated meta-analysis of case-control studies. Asian Pacific journal of cancer prevention: APJCP. -2012. -Vol. 13(6). -P. 2459–2465.

23. Xuhong Dang, Haipeng Lin, Youchen Li, Xiuli Guo, Yayi Yuan, Ruifeng Zhang, Xiaozhen Li, Dongliang Chai, Yahui Zuo. MicroRNA profiling in BEAS-2B cells exposed to alpha radiation reveals potential biomarkers for malignant cellular transformation, Toxicology Research. -2020. -Vol. 9, Issue 6. -P. 834–844.

24. Wu J., Sun B., Zhang S., Zhang J., Tong J., Nie J., Li J. Effects of radon on miR-34a-induced apoptosis in human bronchial epithelial BEAS-2B cells. Journal of toxicology and environmental health. Part A. -2019. -Vol. 82(16). -P. 913–919.

25. Chen H., Chen N., Li F., Sun L., Du J., Chen Y., Cheng F., Li Y., Tian S., Jiang Q., Cui F., Tu Y. Repeated radon exposure induced lung injury and epithelial-mesenchymal transition through the PI3K/AKT/mTOR pathway in human bronchial epithelial cells and mice. Toxicology letters. -2020). -Vol. 334. -P. 4–13.

26. Bulgakova O., Kussainova A., Kakabayev A., Aripova A., Baikenova G., Izzotti A., Bersimbaev R. The level of free-circulating mtDNA in patients with radon-induced lung cancer. Environmental Research, 112215, -2021.

27. Liu J., Liu T., Wang X., He A. Circles reshaping the RNA world: from waste to treasure. Molecular Cancer. -2017. -Vol. 16(1). -P. 58.

28. Lv C., Sun L., Guo Z., Li H., Kong D., Xu B., Lin L., Liu T., Guo D., Zhou J. and Li Y.: Circular RNA regulatory network reveals cell-cell crosstalk in acute myeloid leukemia extramedullary infiltration. J Transl Med. 16:3612018.

29. Zhang H., Deng T., Ge S., Liu Y., Bai M., Zhu K., Fan Q., Li J., Ning T., Tian F., et al: Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7. Oncogene. -2019. 38:2844–2859.

30. Sun X., Wang L., Ding J., Wang Y., Wang J., Zhang X., Che Y., Liu Z., Zhang X., Ye J. et al (2016) Integrative analysis of Arabidopsis thaliana transcriptomics reveals intuitive splicing mechanism for circular RNA. FEBS Lett 590: 3510-3516.

31. Salzman J., Gawad C., Wang P.L., Lacayo N., Brown P.O. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. -2012. -Vol. 7(2).

-p. e30733.

32. Zhong Y., Du Y., Yang X., Mo Y., Fan C., Xiong F., Ren D., Ye X., Li C., Wang Y., et al: Circular RNAs function as ceRNAs to regulate and control human cancer progression. Mol Cancer. 17:79,2018.

33. Wei H., Pan L., Tao D., Li R. Circular RNA circZFR contributes to papillary thyroid cancer cell proliferation and invasion by sponging miR-1261 and facilitating C8orf4 expression. Biochemical and biophysical research communications. -2018. -Vol. 503(1). -P. 56–61.

34. Ding W., Shi Y., Zhang H. Circular RNA circNEURL4 inhibits cell proliferation and invasion of papillary thyroid carcinoma by sponging miR-1278 and regulating LATS1 expression. American journal of translational research. -2021. -Vol. 13(6). -P. 5911–5927.

35. Song W., Wang W.J., Fu T., Chen L., Miao D.L. Integrated analysis of circular RNA-associated ceRNA network in pancreatic ductal adenocarcinoma. Oncology letters. -2020. -Vol. 19(3). -P. 2175–2184.

36. Zhang X., Yang D., Wei Y. Overexpressed CDR1as functions as an oncogene to promote the tumor progression via miR-7 in non-small-cell lung cancer. OncoTargets and therapy. -2018). -Vol. 11. -P. 3979–3987.

37. Ma X., Yang X., Bao W., Li S., Liang S., Sun Y., Zhao Y., Wang J., Zhao C. Circular RNA circMAN2B2 facilitates lung cancer cell proliferation and invasion via miR-1275/FOXK1 axis. *Biochemical and biophysical research communications*. -2018. -Vol. 498(4). -P. 1009–1015.

38. Wang X., Zhu X., Zhang H., Wei S., Chen Y., Chen Y., Wang F., Fan X., Han S., Wu G. Increased circular RNA hsa_circ_0012673 acts as a sponge of miR-22 to promote lung adenocarcinoma proliferation. *Biochemical and biophysical research communications.* -2018. -Vol. 496(4). -P. 1069–1075.

39. Qu D., Yan B., Xin R., Ma T. A novel circular RNA hsa_circ_0020123 exerts oncogenic properties through suppression of miR-144 in non-small cell lung cancer. American journal of cancer research. -2018. -Vol. 8(8). -P. 1387–1402.

40. Zhang Y., Zhao H., Zhang L. Identification of the tumor-suppressive function of circular RNA FOXO3 in non-small cell lung cancer through sponging miR-155. *Mol Med Rep*. -2018. -Vol. 17(6). -P. 7692-7700. doi:10.3892/mmr.2018.8830.

41. Luo Y.H., Zhu X.Z., Huang K.W., Zhang Q., Fan Y.X., Yan P.W., Wen J. Emerging roles of circular RNA hsa_circ_0000064 in the proliferation and metastasis of lung cancer. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. -2017. -Vol. 96. -P. 892–898.

42. Li Y., Hu J., Li L., Cai S., Zhang H., Zhu X., Guan G., Dong X. Upregulated circular RNA circ_0016760 indicates unfavorable prognosis in NSCLC and promotes cell progression through miR-1287/GAGE1 axis. *Biochemical and biophysical research communications*. -2018. -Vol. 503(3). -P. 2089–2094.

43. Liu G., Shi H., Deng L., Zheng H., Kong W., Wen X., Bi H. Circular RNA circ-FOXM1 facilitates cell progression as ceRNA to target PPDPF and MACC1 by sponging miR-1304-5p in non-small cell lung cancer. Biochemical and biophysical research communications. -2019. -Vol. 513(1). -P. 207–212.

44. Li Y., Zou L., Chu L., Ye L., Ni J., Chu X., Guo T., Yang X., Zhu Z. Identification and Integrated Analysis of circRNA and miRNA of Radiation-Induced Lung Injury in a Mouse Model. Journal of inflammation research. -2021. -Vol. 14. -P. 4421–4431.

45. Luo J., Zhang C., Zhan Q. et al. Profiling circRNA and miRNA of radiation-induced esophageal injury in a rat model. Sci Rep. -2018. -Vol. 8. -P. 14605.

Зумама Халид
Медицина ғылымдары бөлімі, Генуя, Италия

Радон тудырған өкпе ісігі үшін жаңа молекулалық биомаркер ретіндегі circRNAs

Аңдатпа. CircRNAs кодталмаған тұйық РНҚ молекулалары болып табылады. Адам ісіктерін, соның ішінде өкпе обырын зерттеу circRNAs а экспрессиялық профилінің өзгеруін көрсетті. circRNAs miRNA функцияларымен байланысу және тежеу арқылы ген экспрессиясын жанама түрде реттей алады. Осы механизм арқылы circRNAs пролиферацияны, апоптозды, инвазияны және метастазды реттей алады. Мақалада біз circRNAs-тың экспрессиясы мен функциясының қысқаша сипаттамасын, сондай-ақ олардың өкпе ісігінің дамуындағы әртүрлі рөлдерін көрсетеміз. Біз молекулаларды радон тудырған өкпе ісігі үшін пайдалы биомаркерлер ретінде зерттеу керек екендігі туралы дәлелдер келтіреміз.

Түйін сөздер: circRNAs, микроРНҚ, өкпе обыры, биомаркерлер, радон.

Зумама Халид
Департамент медицинских наук, Генуя, Италия

CircRNAs как новый молекулярный биомаркер рака легких, вызванного радоном

Аннотация. CircRNAs представляют собой некодирующие замкнутые молекулы РНК. Исследования опухолей человека, включая рак легких, показали изменение профиля экспрессии circRNAs a. circRNAs может косвенно регулировать экспрессию генов путем связывания и ингибирования функций микроРНК. Благодаря этому механизму circRNAs способны регулировать пролиферацию, апоптоз, инвазию и метастазирование. В этом обзоре мы покажем краткое описание экспрессии и функции circRNAs, а также их различных ролей в развитии рака легких. Мы представляем доказательства того, что эти молекулы следует изучать в качестве полезных биомаркеров рака легких, вызванного радоном.

Ключевые слова: circRNAs, микроРНК, рак легкого, биомаркеры, радон.

References

1. Siddiqui F., Siddiqui A.H. Lung Cancer. [Updated 2021 Sep 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls.

2. Reck M., Kerr K.M., Grohé C., Manegold C., Pavlakis N., Paz-Ares L., Huber R.M., Popat S., Thatcher N., Park K., Hilberg F., Barrueco J., Kaiser R. Defining aggressive or early progressing nononcogene-addicted non-small-cell lung cancer: a separate disease entity? Future Oncol. 15(12), 1363-1383(2019).

3. Chang J.H., Lai T.C., Yang P.J. et al. Associations of TIMP-3 Genetic Polymorphisms with EGFR Statuses and Cancer Clinicopathologic Development in Lung Adenocarcinoma Patients. Int J Mol Sci. 2020;21(21):8023., Xu, Shuguang MDa,b; Ying, Kejing MDa,∗ Association between HIF-1α gene polymorphisms and lung cancer, Medicine: June 12. 99(24), e20610(2020).

4. Sengupta D., Banerjee S., Mukhopadhyay P. et al. A comprehensive meta-analysis and a case-control study give insights into genetic susceptibility of lung cancer and subgroups. Sci Rep. 11, 14572(2021).

5. Pasquale R., Forgione L., Roma C., Fenizia F, Bergantino F., Rachiglio A.M., De Luca A., Gallo M., Maiello M.R., Palumbo G., Morabito A., Azzaro R., Normanno N. Targeted sequencing

analysis of cell-free DNA from metastatic non-small-cell lung cancer patients: clinical and biological implications. Transl Lung Cancer Res. 9(1), 61-70(2020).

6. Gou Q., Zhang C.Z., Sun Z.H., Wu L.G., Chen Y., Mo Z.Q., Mai Q.C., He J., Zhou Z.X., Shi F., Cui W., Zou W., Lv L., Zhuang W.H., Xu R.D., Li W.K., Zhang J., Du H.W., Xiang J.X., Wang H.Z., Hou T., Li S.T., Li Y., Chen X.M., Zhou Z.J. Cell-free DNA from bile outperformed plasma as a potential alternative to tissue biopsy in biliary tract cancer. ESMO Open. 6(6), 100275(2021).

7. Duan X., Qiao S., Li D., Li S., Zheng Z., Wang Q., Zhu X. Circulating miRNAs in Serum as Biomarkers for Early Diagnosis of Non-small Cell Lung Cancer. Front Genet. 12, 673926(2021).

8. Dama E., Colangelo T., Fina E., Cremonesi M., Kallikourdis M., Veronesi G., Bianchi F. Biomarkers and Lung Cancer Early Detection: State of the Art. Cancers (Basel). 2021 Aug 3;13(15):3919.

9. Shankar A., Dubey A., Saini D. et al. Environmental and occupational determinants of lung cancer. Transl Lung Cancer Res. 8(1), S31-S49(2019).

10. Dela Cruz C.S., Tanoue L.T., & Matthay R.A. Lung cancer: epidemiology, etiology, and prevention. Clinics in chest medicine. 32(4), 605–644(2011).

11. Bechara E.G., Sebestyén E., Bernardis I., Eyras E., Valcárcel J. RBM5, 6, and 10 differentially regulate NUMB alternative splicing to control cancer cell proliferation. Molecular cell. 52(5), 720–733(2013).

12. Lu L., Xu H., Luo F., Liu X., Lu X., Yang Q., Xue J., Chen C., Shi L., Liu Q. Epigenetic silencing of miR-218 by the lncRNA CCAT1, acting via BMI1, promotes an altered cell cycle transition in the malignant transformation of HBE cells induced by cigarette smoke extract. Toxicology and applied pharmacology. 304, 30–41(2016).

13. Rivera G.A., Wakelee H. Lung Cancer in Never Smokers. Advances in experimental medicine and biology. 893, 43–57(2016).

14. Hubaux R., Becker-Santos D.D., Enfield K.S., Lam S., Lam W.L., Martinez V.D. Arsenic, asbestos, and radon: emerging players in lung tumorigenesis. Environ Health. 2012;11:89.

15. Azara A., Dettori M., Castiglia P., Piana A., Durando P., Parodi V., Salis G., Saderi L., Sotgiu G. Indoor Radon Exposure in Italian Schools. International journal of environmental research and public health. 15(4), 749(2018).

16. U.S. Environmental Protection Agency. Radon health risks. Washington D.C.: U.S. Environmental Protection Agency. 2012.

17. Lorenzo-González M., Ruano-Ravina A., Torres-Durán M., Kelsey K.T., Provencio M., Parente-Lamelas I., Leiro-Fernández V., Vidal-García I., Castro-Añón O., Martínez C., Golpe-Gómez A., Zapata-Cachafeiro M., Piñeiro-Lamas M., Pérez-Ríos M., Abal-Arca J., Montero-Martínez C., Fernández-Villar A., & Barros-Dios J.M. Lung cancer and residential radon in never-smokers: A pooling study in the Northwest of Spain. Environmental research. 172, 713–718(2019).

18. Hubaux R., Becker-Santos D.D., Enfield K.S., Lam S., Lam W.L., Martinez V.D. Arsenic, asbestos, and radon: emerging players in lung tumorigenesis. Environ Health. 2012;11:89.

19. Vähäkangas K.H., Samet J.M., Metcalf R.A., Welsh J.A., Bennett W.P., Lane D.P. & Harris C.C. Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. Lancet (London, England). 339(8793), 576–580(1992).

20. Gogna P., Narain T.A., O'Sullivan D.E., Villeneuve P.J., Demers P.A., Hystad P., Brenner D.R., Friedenreich C.M., King W.D. & ComPARe Study Team. Estimates of the current and future burden of lung cancer attributable to residential radon exposure in Canada. Preventive medicine. 122, 100–108(2019).

21. Torres-Durán M., Ruano-Ravina A., Parente-Lamelas I., Leiro-Fernández V., Abal-Arca J., Montero-Martínez C., Pena-Álvarez C., González-Barcala F.J., Castro-Añón O., Golpe-Gómez A., Martínez C., Mejuto-Martí M.J., Fernández-Villar A. & Barros-Dios J.M. Lung cancer in never-smokers:

a case-control study in a radon-prone area (Galicia, Spain). The European respiratory journal. 44(4), 994–1001(2014).

22. Zhang Z.L., Sun J., Dong J.Y., Tian H.L., Xue L., Qin L.Q., Tong J. Residential radon and lung cancer risk: an updated meta-analysis of case-control studies. Asian Pacific journal of cancer prevention: APJCP. 13(6), 2459–2465(2012).

23. Xuhong Dang, Haipeng Lin, Youchen Li, Xiuli Guo, Yayi Yuan, Ruifeng Zhang, Xiaozhen Li, Dongliang Chai, Yahui Zuo. MicroRNA profiling in BEAS-2B cells exposed to alpha radiation reveals potential biomarkers for malignant cellular transformation, Toxicology Research. 9(6), 834–844(2020).

24. Wu J., Sun B., Zhang S., Zhang J., Tong J., Nie J., Li J. Effects of radon on miR-34a-induced apoptosis in human bronchial epithelial BEAS-2B cells. Journal of toxicology and environmental health. Part A. 82(16), 913–919(2019).

25. Chen H., Chen N., Li F., Sun L., Du J., Chen Y., Cheng F., Li Y., Tian S., Jiang Q., Cui F., Tu Y. Repeated radon exposure induced lung injury and epithelial-mesenchymal transition through the PI3K/AKT/mTOR pathway in human bronchial epithelial cells and mice. Toxicology letters. 334, 4–13(2020).

26. Bulgakova O., Kussainova A., Kakabayev A., Aripova A., Baikenova G., Izzotti A., Bersimbaev R. The level of free-circulating mtDNA in patients with radon-induced lung cancer. Environmental Research, 112215(2021).

27. Liu J., Liu T., Wang X., He A. Circles reshaping the RNA world: from waste to treasure. Molecular Cancer. 16(1), 58(2017).

28. Lv C., Sun L., Guo Z., Li H., Kong D., Xu B., Lin L., Liu T., Guo D., Zhou J. and Li Y. Circular RNA regulatory network reveals cell-cell crosstalk in acute myeloid leukemia extramedullary infiltration. J Transl Med. 16:3612018.

29. Zhang H., Deng T., Ge S., Liu Y., Bai M., Zhu K., Fan Q., Li J., Ning T., Tian F., et al: Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7. Oncogene. 38, 2844–2859(2019).

30. Sun X., Wang L., Ding J., Wang Y., Wang J., Zhang X., Che Y., Liu Z., Zhang X., Ye J. et al. Integrative analysis of Arabidopsis thaliana transcriptomics reveals intuitive splicing mechanism for circular RNA. FEBS Lett. 590, 3510-3516(2016).

31. Salzman J., Gawad C., Wang P.L., Lacayo N., Brown P.O. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 7(2), e30733(2012;.

32. Zhong Y., Du Y., Yang X., Mo Y., Fan C., Xiong F., Ren D., Ye X., Li C., Wang Y., et al: Circular RNAs function as ceRNAs to regulate and control human cancer progression. Mol Cancer. 17, 79(2018).

33. Wei H., Pan L., Tao D., Li R. Circular RNA circZFR contributes to papillary thyroid cancer cell proliferation and invasion by sponging miR-1261 and facilitating C8orf4 expression. Biochemical and biophysical research communications. 503(1), 56–61(2018).

34. Ding W., Shi Y., Zhang H. Circular RNA circNEURL4 inhibits cell proliferation and invasion of papillary thyroid carcinoma by sponging miR-1278 and regulating LATS1 expression. American journal of translational research. 13(6), 5911–5927(2021).

35. Song W., Wang W.J., Fu T., Chen L., Miao D.L. Integrated analysis of circular RNA-associated ceRNA network in pancreatic ductal adenocarcinoma. Oncology letters. 19(3), 2175–2184(2020).

36. Zhang X., Yang D., Wei Y. Overexpressed CDR1as functions as an oncogene to promote the tumor progression via miR-7 in non-small-cell lung cancer. OncoTargets and therapy. 11, 3979–3987(2018).

37. Ma X., Yang X., Bao W., Li S., Liang S., Sun Y., Zhao Y., Wang J., Zhao C. Circular RNA circMAN2B2 facilitates lung cancer cell proliferation and invasion via miR-1275/FOXK1 axis. *Biochemical and biophysical research communications*. *498*(4), 1009–1015(2018).

38. Wang X., Zhu X., Zhang H., Wei S., Chen Y., Chen Y., Wang F., Fan X., Han S., Wu G. Increased circular RNA hsa_circ_0012673 acts as a sponge of miR-22 to promote lung adenocarcinoma proliferation. *Biochemical and biophysical research communications. 496*(4), 1069–1075(2018).

39. Qu D., Yan B., Xin R., Ma T. A novel circular RNA hsa_circ_0020123 exerts oncogenic properties through suppression of miR-144 in non-small cell lung cancer. American journal of cancer research. 8(8), 1387–1402(2018).

40. Zhang Y., Zhao H., Zhang L. Identification of the tumor-suppressive function of circular RNA FOXO3 in non-small cell lung cancer through sponging miR-155. *Mol Med Rep*. 17(6), 7692-7700(2018). doi:10.3892/mmr.2018.8830.

41. Luo Y.H., Zhu X.Z., Huang K.W., Zhang Q., Fan Y.X., Yan P.W., Wen J. Emerging roles of circular RNA hsa_circ_0000064 in the proliferation and metastasis of lung cancer. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 96, 892–898(2017).

42. Li Y., Hu J., Li L., Cai S., Zhang H., Zhu X., Guan G., Dong X. Upregulated circular RNA circ_0016760 indicates unfavorable prognosis in NSCLC and promotes cell progression through miR-1287/GAGE1 axis. *Biochemical and biophysical research communications*. 503(3), 2089–2094(2018).

43. Liu G., Shi H., Deng L., Zheng H., Kong W., Wen X., Bi H. Circular RNA circ-FOXM1 facilitates cell progression as ceRNA to target PPDPF and MACC1 by sponging miR-1304-5p in non-small cell lung cancer. Biochemical and biophysical research communications. 513(1), 207–212(2019).

44. Li Y., Zou L., Chu L., Ye L., Ni J., Chu X., Guo T., Yang X., Zhu Z. Identification and Integrated Analysis of circRNA and miRNA of Radiation-Induced Lung Injury in a Mouse Model. Journal of inflammation research. 14, 4421–4431(2021).

45. Luo J., Zhang C., Zhan Q. et al. Profiling circRNA and miRNA of radiation-induced esophageal injury in a rat model. Sci Rep. 8, 14605(2018).

Information about author:

Халид Зумама – Генуя университетінің медицина ғылымдары факультетінің 1 курс докторанты, Генуя, Италия.

Khalid Zumama – The 1st year doctoral student, Department of Helth Science, University of Genova, Genova, Italy.