Editorial Commentary

New promising circulating RNA biomarkers for early diagnosis of lung adenocarcinoma

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Clinical practice relies in the use of specific biological parameters which can be correlated with the onset, establishment, development and therapeutic response of diseases. Biomarkers have becoming even a more relevant research topic in clinics since the foundation of the precision medicine initiatives worldwide. The choice of specific biomarkers is dependent on their sensitivity and specificity for a particular disease, but also on technical aspects related with their collection protocol, stability and detection from biological samples. In clinical oncology, early diagnosis biomarkers are very important for the prevention of the incidence of cancers, but also for the establishment of proper therapeutic strategies.

The dynamic genomic output in the form of RNA molecules is a fingerprint of the physiological state of cells. In cancer cells, the dysregulation of transcriptional programs is within the core of the tumor establishment and progression and could be used for diagnosis and prognosis in clinical practice. Among the myriad of RNA molecules produced from the genome, the non-coding RNAs (ncRNAs) are recognized as essential players in tumorigenesis. These ncRNAs included several molecular families ranging from the size of a few nucleotides to kilobases in length. Typically, ncRNAs are originated from the transcription and further processing of specific transcriptional units within the genome, with the exception of circular-RNAs (circRNAs) which are originated by non-canonical splicing events of RNA transcripts originated from already established transcriptional units, either protein-coding or ncRNAs (1). circRNAs are a wide family of ncRNA molecules engaged in regulatory networks that involve functional interactions with other biomolecules such as proteins or nucleic acids, being considered as central players in the establishment of regulatory events that will lead to changes in cellular fate and physiology (2,3). In the context of cancer, circRNAs have been described as relevant players not only for their ability to regulate the function of other molecules (4) but also because of their direct involvement in tumorigenesis (5). Cancer cells showed aberrant profiles of circRNA expression when compared with normal ones, which could be used as biomarkers to characterize the tumor state and progression (6,7). Interestingly, circRNAs are actively secreted by normal and cancer cells and can be found in biofluids together with other ncRNAs such as microRNAs (miRNAs) mainly associated with extracellular vesicles (8-10). The possibility of a non-invasive sample collection for biomarker assays by the obtention of biofluids from the patient and further quantification of circRNAs, opens a new avenue for the discovery and use oncological biomarkers that could accelerate the establishment of the general postulates of personalized medicine in clinical practice (7,11). Compared with other circulating ncRNAs, circRNAs have clear advantages to be used as biomarkers since they

have the tendency to be more specific than other ncRNAs and also because their circular structure that turns them more stable to degradation by nucleases (6). Moreover, circRNAs quantification from biofluids is based on the use of quantitative PCR with specific divergent primers which could be easily implemented within the analytical pipelines established in small and big clinical units.

Lung cancer is one of the most prevalent and aggressive tumors in western countries, characterized by a high morbidity and mortality due to its potential metastatic capabilities. Current diagnostic techniques for lung cancer are mainly based on imaging of lung tissue, which requires an obvious proliferating tumor mass and will often needs to be followed by a differential diagnosis to distinguish primary lung tumors from other conditions such as infectious granulomas or metastatic lesions from other cancers. In consequence, there is a current unmet medical need for early diagnostic biomarkers for lung cancer that could provide appropriate differential diagnosis of the condition, prevent the tumor progression from initial stages, and help the physicians to establish effective and reliable therapeutic strategies (12).

The manuscript by Liu and coworkers (13) describes how an already published information can be used to derive useful and relevant clinical information. The authors relied on previously published data to determine a characteristic signature of differentially expressed circRNAs in lung cancer samples when compared with adjacent healthy cells (14). Taking into account the assumption that overexpressed circRNAs in lung cancer cells could be potentially secreted to peripheral blood, the authors validated the presence of the differentially expressed circRNAs in the plasma of a cohort of histologically stratified patients with lung adenocarcinoma (83 were in stage I, 13 in stage II, 30 in stage III, and 25 in stage IV). The subsequent work identified a circulating circRNAs biomarker signature composed by two upregulated (hsa_circ_0005962 and hsa_circ_0003958) and two downregulated circRNAs (hsa_circ_0086414 and hsa_circ_0001936) with prognostic value in lung adenocarcinoma. The group of over-expressed circulating circRNAs, hsa_circ_0005962 and hsa_circ_0003958, was also used to determine their prognostic value as post-surgery biomarkers. In this context, the hsa_circ_0005962 plasma level was decreased in 42 of the 54 (77.78%) lung adenocarcinoma patients after surgery whereas no significant difference in hsa_circ_0086414 levels was observed between the pre-operative and post-operative stages. Interestingly, hsa_circ_0005962 is generated by non-canonical splicing of mRNA transcripts originated from *YWHAZ* gene. Over-expression of *YWHAZ* genes has been already related with tumor malignancy in other cancers such as the gastric adenocarcinoma, being associated with a worse outcome characterized by an increased invasiveness (15). Also in esophageal adenocarcinomas, the over-expression of *YWHAZ* gene has been independently characterized as a negative prognosis factor (16). On the other hand, hsa_circ_0086414 is a product of back-splicing of a coding transcript generated from *BNC2* gene, which has been characterized as a tumor suppressor in ovarian cancer (17). In hepatocellular carcinoma is frequent to observe patients with a *BNC2* gene deletion, which may suggest that the expression of *BNC2* might be an important regulatory point for the tumor establishment and progression (18).

Despite of the lack of knowledge about the subjacent molecular mechanisms involved in the secretion of circRNAs by cancer cells, there is increased evidence about their use as molecular circulating biomarkers for the stratification and prognosis of tumors, as illustrated by this relevant example applied to lung adenocarcinoma. The introduction of these new molecular biomarkers in the routine of the clinical practice is clearly dependent on the compilation of increased amounts of translational data, that will allow the physicians to consider their implementation into the practical guidelines.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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