Circulating miRNA signature for early diagnosis of lung cancer

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. Despite the numerous recent studies on NSCLC genomics, molecular mechanisms of disease and the development of targeted therapies, which improve treatment responses to a certain extent, the overall 5-year survival rate is only around 10–15%. The main reason for such a low 5-year survival rate has long been attributed to late diagnosis of the disease in three quarters of patients, resulting in advanced and inoperable diseases. Lung cancer studies for decades have attempted to develop screening modalities that allow early diagnosis. However, in contrast to the success in prognostic and predictive biomarker research during the past 10 years, the progress in early lung cancer screening is still limited and restricted to imaging studies.

Chest radiography and sputum cytology screening programs in the 1970s had failed to reduce cancer mortality. Low-dose spiral chest computed tomography (LDCT) screening trials carried out in the 2000s generally resulted in a significant increase in the number of early-stage lung cancer diagnoses, but without apparent reduction in development of advanced cancers or cancer mortality (Pastorino, 2010). The first successful large LDCT screening trial reported is the National Lung Screening Trial (NSLT). It demonstrates a 20% reduction of cancer mortality in the LDCT screening arm compared to the chest radiography arm (http://www.cancer.gov).

The results from these LDCT screening studies highlight several issues worth noticing. First, LDCT leads to over-diagnosis of benign/indolent pulmonary lesions and cause significant increase of unnecessary surgical intervention (Bach, 2008). This makes non-invasive biomarkers a desperate need in order to help differentiate malignant lesions from the benign, which are detected by the sensitive LDCT. Second, the annual LDCT screening studies show that if cases are diagnosed in the latter half of the screening period, instead of during the first 2 years of screening, the disease is more likely to be aggressive with fast-growing tumours and poor prognosis. These findings support the assumption that argues against the traditional lung cancer natural history model, that perhaps not all aggressive lung cancers arise from identifiable slow-growing precursors. This further strengthens the importance and necessity of developing sensitive biomarkers to discriminate the aggressive from the indolent and to detect the tumour's existence before visualization is possible.

Microribonucleic acids (miRNAs) are small non-coding, endogenous, single-stranded ribonucleic acids (RNAs) that regulate gene expression and are involved in the regulation of many important pathways, including developmental and oncogenic pathways (Bartel, 2004). They are tissue-specific as well as frequently dysregulated in cancers and are thus considered potential cancer biomarkers. Previous studies on NSCLCs using tissue-derived miRNAs show that they are capable of classifying histology subtypes, predict prognosis and disease recurrence in early-stage NSCLCs (Lin et al, 2010; Yu et al, 2008). Unlike messenger RNAs (mRNAs), which are vulnerable and easily degraded by ribonucleases, miRNAs are found not only to be stable in paraffin-embedded tissues and body fluids, but also in plasma and serum (Mitchell et al, 2008). Their accessibility makes circulating miRNAs attractive in the era of personalized cancer therapy.

In this issue of EMBO Molecular Medicine, Bianchi et al report a 34 circulating miRNA signature, which is able to identify asymptomatic high-risk individuals with early lung cancer and distinguish malignant lesions from benign nodules revealed by LDCT (Bianchi et al, 2011). They used serum from 93 patients enrolled in the COSMOS study who were diagnosed with NSCLC in the first 2 years of screening, and serum from 69 individuals who were not found to have cancers by LDCT during the entire study as controls. The cases and controls were divided into a training set (25 adenocarcinoma patients and 39 normal controls) and a testing set (22 adenocarcinoma patients, 12 squamous cell carcinoma patients, and 30 normal controls). The selected 34 miRNAs were weighed

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according to their accuracy in predicting diagnosis and then linearly combined into a risk score. The risk score derived from the 34-miRNA signature was shown to differentiate high risk from low risk patients in both adenocarcinoma and squamous cell carcinoma of all stages with 80% accuracy, and is able to differentiate between the malignant and the benign lesions detected by LDCT. This signature has been validated in another independent cohort with similar success rate.

The findings by Bianchi and colleagues support and confirm the results of Boeri et al published earlier this year (Boeri et al, 2011). Boeri and colleagues used the INT-IEO cohort as training set and the MILD cohort as validation set. They report a 13 circulating miRNA diagnostic signature of NSCLC that can differentiate aggressive from indolent tumours detected by LDCT with approximately 80% accuracy. They further showed that the signature actually appears months before NSCLC can be diagnosed by LDCT in patients whose tumours presented with aggressive clinical behaviour. Of note, this subgroup of patients happened to be those diagnosed by LDCT in the 3rd to 5th year, instead of in the first 2 years of LDCT screening program.

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The results reported by the two groups have important clinical implications. They both demonstrated that non-invasive circulating miRNA signatures are able to distinguish between malignant and benign lesions on LDCT, and to differentiate the aggressive subgroup among the entire population of enrolled patients. This represents an important step forward in clinical practice as it may reduce unnecessary surgical intervention and has the potential to serve as a non-invasive screening tool for early lung cancer diagnosis.

Boeri and colleagues also performed miRNA expression profiling in tumours and paired adjacent normal lung. They showed that the profile of tumours detected in the first 2 years of the screening is different from that detected after the 2nd year, which is associated with distinct aggressive features and fast growth rate. Their findings also demonstrated that miRNA expression of normal lung tissues was different in subjects identified in the first 2 years from those of later years of screening, which supports the tumour microenvironment theory. Together with clinical observations, their results may change the traditional dogma in the natural history of NSCLC development and is important both in translational research and clinical practice.

MiRNAs are special because they are stable, tissue-specific, and dysregulated in the diseased organs and cancers. These characteristics make them potential biomarkers in prognostic and predictive purposes. The understanding of their presence and stability in serum/plasma and their promise as non-invasive diagnostic biomarkers are important breakthroughs. These insights facilitate their clinical applications in large-scale and long-term lung cancer screening, monitoring, and tailor-made personalized cancer therapy.

Our knowledge about circulating miRNAs is growing. However, there are still pieces of the puzzle missing, such as the cells of their origin and the suitability of representativeness of total serum/plasma miRNAs versus miRNAs isolated from different vesicular compartments in blood. It will be interesting to see if future studies can answer these questions. Moreover, as in mRNA profiling studies, miRNA signatures identified by different groups can vary from one another. Large prospective cohorts and cross validation are needed to consolidate the important findings demonstrated by the two groups.

In summary, Bianchi, Boeri, and their colleagues present an important breakthrough in the study of early detection of lung cancer. The miRNA diagnostic signatures, in conjunction with, or even independent from the LDCT screening may represent a new milestone in early lung cancer diagnosis.

The authors declare that they have no conflict of interest.

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