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Commentary

Lung Cancer Early Detection: The Role of Circulating MicroRNAs

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Lung cancer screening with low-dose Computed Tomography (LDCT) was recently shown to be effective in reducing lung cancer mortality (Aberle et al., 2011). An ~20% of reduction of mortality was observed at 3 years in the LDCT arm of a randomized multicenter study, the National Lung Cancer Screening Trial (NLST), which enrolled ~53.000 high-risk individuals (>55 years, >30 packs-year) planned to receive annual LDCT or chest X-ray (Aberle et al., 2011). This groundbreaking result occurred after several years of debate about the benefits of LDCT screening in terms of improved early diagnosis and survival, and whether an annual LDCT scan in asymptomatic high-risk individuals should be recommended or not (Field and Duffy, 2008). However, both the high number of individuals who need to be screened to detect one lung cancer patient (~1 patient out of 100 individuals) and the sizeable false-positive rate of LDCT observed in these screening trials (most of the lung nodules detected are benign, ~96%) are limiting the widespread applicability of LDCT screening programs (Aberle et al., 2011). Therefore, there is an urgent need to identify novel biomarkers for the early diagnosis of lung cancer to better identify the high-risk population, thus reducing the number of unnecessary LDCTs for individuals without lung cancer and the rate of false-positive findings.

In this issue of *EBioMedicine*, Wang et al. (2015) describes a new set of biomarkers diagnostic for lung cancer. The authors found that the increased serum levels of 5 microRNAs (miR-483-5p, miR-193a-3p, miR-25, miR-214 and miR-7) in a Chinese cohort of lung cancer patients and healthy individuals were diagnostic for lung cancer. MicroRNAs (miRNAs) are short non-coding RNA molecules involved in the regulation of many cellular processes by acting as endogenous triggers of the mRNA interference pathway (Krol et al., 2010). Importantly, fluctuations of circulating miRNAs were shown to be associated with many malignant and non-malignant diseases, including lung cancer (Chen et al., 2008). Of note, circulating miRNAs are remarkably stable in the blood despite harsh conditions due to the presence of high levels of RNases (Mitchell et al., 2008). Therefore, circulating miRNAs appear to be excellent candidates for blood-borne tumor markers for the diagnosis of cancer.

An important aspect in the present study by Wang et al. is the extensive validation of these miRNA biomarkers in independent cohorts of patients. Indeed, the authors used four independent cohorts of patients and healthy individuals (for a total of 221 NSCLC, 56 with benign nodules, and 161 healthy individuals) to train and validate the 5-miRNA signature. The cohorts were recruited from different health centers (multicentric study) and individuals were of different ethnicity (Chinese and American individuals) to appreciate eventual differences in the basal blood miRNA level, which could negatively affect the diagnostic test performance. These are all very important aspects that should be taken in consideration when designing a screening study for cancer biomarker identification. Indeed, the failure of many proposed cancer biomarkers once validated in clinical trials is mainly ascribable to a poor study design adopted during the discovery phase, which, in most of the cases, did not include cohorts of patients sufficiently large and independent (Poste, 2011).

Other research groups have recently described circulating miRNA signatures in serum and plasma for the early diagnosis of lung cancer, with comparable results in terms of sensitivity and specificity for detecting lung cancer (Sozzi et al., 2014; Montani et al., 2015; Wozniak et al., 2015). Some of these signatures have been already validated in existing lung cancer screening studies (Sozzi et al., 2014; Montani et al., 2015), which is mandatory to assess the accuracy of these diagnostic biomarkers in detecting asymptomatic early-stage lung cancer. It would be interesting to perform a meta-analysis of all of these signatures by using both serum and plasma samples from the same cohort of individuals. This would allow the direct comparison of their diagnostic performance and, eventually, identify a core of biomarkers to increase the overall accuracy of a miRNA-based test for lung cancer early detection.

Conflicts of Interest

None.

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