Current challenges in lung cancer early detection biomarkers

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Lung cancer is a public health challenge in Europe and worldwide. Almost 400,000 new lung cancers were diagnosed and over 330,000 Europeans died of lung cancer in 2006 [1]. The average 5-year survival from lung cancer in Europe is around 15%. Nevertheless, survival from an early stage operable non small cell lung cancer (NSCLC) reaches around 70%. Nowadays, only a third of lung cancer patients are diagnosed at these early operable stages and thus the dismal survival numbers. The decrease in lung cancer mortality will only be achieved if successful strategies are developed in three directions: smoking cessation, early diagnosis and development of new molecular targeted therapies.

Early screening tests for high risk individuals based on sputum cytology or chest X-ray have not shown improvement for disease-specific survival. A chest low-dose computed tomography (CT) scan has been proven as a very effective tool for the detection of early stage resectable disease. However, the potential use of CT as a lung cancer screening tool is still a matter of contention. The ongoing randomised trials will show, in the future, the real impact of early detection on mortality at the population level.

There is an increasing interest in the development of molecular-based non invasive screening methods. The aim is to detect molecular biomarkers in biological fluids before lung cancer symptoms arise. These methods could be extremely useful in the context of CT-based screening protocols for risk stratification, diagnostic reinforcement, biological profiling of the CT-detected nodules, prognostic characterisation or treatment selection. Several papers have reported about lung cancer susceptibility loci using single nucleotide polymorphism (SNP) genome-wide association studies [2]. There are proposals to build quantitative lung cancer risk models based on susceptibility associated genetic markers together with pack years, other environmental exposure indicators and clinical parameters. Several groups, including ours at the University of Navarra, have shown that airway obstruction, chronic inflammation and/or emphysema (a chronic obstructive pulmonary disease) may be useful risk indicators for lung cancer [3].

At this time, there is not a single validated molecular biomarker for lung cancer early detection. Therefore, no biomarker is currently used in parallel to CT-based techniques. Sozzi and colleagues [4] have reported on the analysis of free circulating DNA in a 5-year prospective trial of early lung cancer detection, applying yearly low-dose spiral CT to high risk heavy smokers. According to their conclusions, the measurement of plasma DNA performs very poorly in detecting small adenocarcinomas of the type frequently detected in CT screening series. They suggest that either technical or biological reasons may explain these results, which are in contrast with their previous report for more advanced tumours [5]. We have studied the molecular profile of the tumours found in the I-ELCAP screening series of over 1000 heavy smokers at the Clinica Universidad de Navarra [6].

The field of lung cancer biomarkers is faced with a number of challenges. First, more comprehensive understanding of the molecular alterations during lung carcinogenesis is needed to find new and more robust biomarkers. Second, the diagnostic usefulness of these markers and their detection in biological fluids, like blood or sputum, need to be explored. Finally, techniques for the specific marker detection are to be developed and validated in the clinical setting.

The traditional sources of cancer biomarkers are the analysis of mutations, gene copy number variations (amplifications or deletions), expression alterations and epigenetic regulation. In the last decade, the field has witnessed an impressive shift from single maker interest to the analysis of gene or protein signatures. A catalogue of the most prevalent 26 mutations in lung adenocarcinomas has been published [7]. A number of recent papers inform about gene expression signatures with survival predictive value, unfortunately with very little overlap in the lists of predictive genes [8], somewhat limiting the clinical application of this important information. High resolution (250k) SNP

arrays have also been used to explore the genome of lung adenocarcinoma [9]. This massive information will require impressive data processing tools and very careful interpretation to provide meaningful clinical information.

Our lab is interested in the pre-mRNA processing as an important mechanism for globally modifying cellular protein composition. Through alternative pre-mRNA splicing, several related proteins with diverse and even antagonistic functions may be expressed from a single gene. Alterations in the mRNA processing machinery and aberrant mRNA splicing have been associated with various diseases, including cancer. The analysis of cancer-specific alternative splicing and its biological consequences is a promising field in molecular oncology [10]. We have studied the role of splicing regulators and other RNA-binding proteins such as αCP-4, hnRNP A1 or ASF/SF2 in the biology of lung cancer [11]. We have also designed and developed a whole-genome splicing-specific microarray to search for differentially expressed splicing isoforms in lung cancer.

Finally, I will discuss some of the challenges that we are currently facing in the development of lung cancer biomarkers. A good biomarker has to be detectable in clinically accessible material (serum, sputum, bronchial lavage, exhaled breath condensates ...); a reliable, reproducible and robust assay is required, with standardised methods and gold standard controls; finally, biomarker analyses for which automated platforms are available are the most likely to be successful in large scale clinical settings. At present, no lung cancer early detection biomarker is clinically available. Several candidate biomarkers such as sputum methylation analysis [12], panels of serum proteins [13], exfoliated airway epithelial cell gene signature [14], or lung cancer associated autoantibodies [15] are still at the very early phases in the ladder of clinical validation of cancer biomarkers [16]. Ways to overcome current bottlenecks to speed up the development of lung cancer early detection biomarkers will be discussed.

Conflict of interest statement

None declared.

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