

Metabolomics approach applied to exhaled breath condensate in lung cancer

Mauro Maniscalco, Salvatore Fuschillo

INTRODUCTION

Several studies on lung cancer research have been performed with the aim of revealing biomarkers representative of the cancer phenotype as well as possible therapeutic targets. This has led to the identification of many molecular features involved in lung cancer with new biochemical adaptations in the carcinogenetic process with quantitative changes in endogenous metabolites [1]. Recently, omics sciences have arising interest in cancer research as they could potentially detect new biomarkers, improving disease diagnosis and evaluating the effect of the treatment [2].

Among all omics, metabolomics is currently, one of the fastest developing disciplines in cancer research. In fact, metabolomics is the comprehensive assessment of endogenous metabolites (metabolome) and attempts to systematically identify and quantify metabolites from a biological specimen in a both global and targeted manner [3, 4]. The application of metabolomics to cancer is increasing year by year in the search for candidate biomarkers that define a particular cancer, whose directional variation is significantly higher than all other endogenous metabolites that comprise the complex sample for analysis.

Metabolomics methods usually use nuclear magnetic resonance (NMR) and mass spectrometry (MS). Nuclear magnetic resonance spectroscopy can be considered as a universal metabolite detection technique. Nuclear magnetic resonance studies molecules by recording the interaction of radiofrequency electromagnetic radiation with the nuclei placed in a strong magnetic field [5]. Mass

spectrometry consists in producing gas-phase ions that are further detected and characterized by their mass and charge [6].

Although metabolomics analyses may be applied to several biological matrix such as plasma, urine sputum, the respiratory tract offers a natural matrix, the exhaled breath, which appears well suited for the metabolomics studies [7–10]. In fact exhaled breath condensate (EBC), obtained by cooling exhaled air from spontaneous tidal breathing, represent a non-invasive method of collecting samples of the airway-lining fluid on which metabolomics methodology can be fruitfully applied [11].

EXHALED BREATH CONDENSATE METABOLOMICS AND LUNG CANCER

Recently, metabolomics-based analysis has been applied to exhaled breath condensate in lung cancer. In 2016, Peralbo-Molina et al. [12] applied metabolomics analysis on EBC to discriminate between patients with lung cancer and those at risk for lung cancer. Untargeted analysis, using gas chromatography time-of-flight mass spectrometry, was conducted in a cohort of patient with lung cancer, risk factor individuals (active smokers and ex-smokers) and control healthy individuals in order to detect the EBC metabolic signature within risk and cancer affected individuals. Five compounds were significant in the comparison of the lung cancer patients versus the risk factor group. Among these compounds it is worth noting the presence of two saturated monoacylglycerols (monopalmitin and monostearin) and an acyclic triterpenoid (squalene). Monopalmitin and monostearin were characterized by different behaviors: monopalmitin was more concentrated in the risk factor group than the cancer group. On the other hand, monostearin offered an inverse profile, as the risk factor group showed a lower relative concentration than the lung cancer patients.

Subsequently, the same authors identified metabolomics panels for potential lung cancer screening. Metabolite profiles were obtained from lung cancer patients, which were compared to those provided by two additional cohorts: a risk factor group formed by active smokers with at least 20 pack-years of exposure and

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ex-smokers and a second group including healthy non-smoker individuals. Exhaled breath condensate collected from the three groups of subjects was analyzed. The best panel of metabolites with capability of discrimination between the risk factor cohort and healthy individuals was formed by combination of five metabolites providing a 90.3% specificity, 77.9% sensitivity and 85.1% AUC. Discrimination of lung cancer patients versus the risk factor individuals resulted in one other five-compound panel characterized by sensitivity close to 90%, and a specificity of nearly 70% [13].

Furthermore, in this study, the subjects with the most common lung cancer diagnosis (squamous cell carcinoma and adenocarcinoma) were selected to compare their EBC composition with the aim of identify metabolomics differences among lung cancer stages. The authors found that five of these compounds which have benzoic structure with alkyl groups and which could be related to tobacco smoke, were present in the patients with advanced cancer stage.

In another study, Ahmed et al. aimed to determine if H1 MRS of sputum and EBC can identify biomarkers of lung cancer. In the EBC samples, median concentrations some metabolites (propionate, ethanol, acetate, and acetone) were higher in lung cancer patients compared to the patients with benign conditions [14].

CONCLUSION

Metabolomics applied to exhaled breath condensate (EBC) might represent an important tool for diagnostics, management and follow-up of lung cancer in the future. The development of a series of analytical platforms capable of accurately measuring hundreds or thousands of small molecules in biological samples and specifically in EBC, promises to advance our pathophysiological understanding of lung cancer, identifying early metabolic changes in disease provide an opportunity to develop predictive biomarkers that can trigger earlier interventions.

Keywords: Biomarkers, Lung cancer, Metabolomics

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Mauro Maniscalco – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Salvatore Fuschillo – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

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Conflict of Interest

Authors declare no conflict of interest.

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