

Biomarkers in allergic asthma: Which matrix should we use?

Dear Editor,

We have read with great interest the review article by Villaseñor et al.¹ on metabolomics strategies for the identification of novel biomarkers associated with specific phenotypes of allergic asthma. The paper also suggests the usefulness of specific biological matrices in the metabolomics approach to respiratory pathologies, indicating preferentially bronchoalveolar lavage fluid (BALF), lung biopsy or sputum for exploratory studies on molecular mechanism of a respiratory disease, and plasma or urine for detecting diagnostic or prognostic biomarkers. Surprisingly, the authors do not include the exhaled breath condensate (EBC) as suitable matrix. In fact, they state that although "EB is a relevant sample in respiratory affections because it shows the characteristic compounds from lung metabolism, its greatest handicap is the difficulty to obtain a reliable interpretation and correlation of these metabolites with the (asthma) disease".¹

Asthma is a complex and heterogeneous pathology linked to mechanisms that are not present in all patients at any given time-point or in the same patient at different time-points, and these features call for the characterization of asthma-specific phenotypes. A phenotype can be defined by a single or multiple domains (clinical characteristics and specific cellular patterns in biological samples) in which metabolic profiles and the corresponding metabolic pathways differ according to the biological matrix considered.² Accordingly, in an animal model, NMR-based profiling studies on different biological matrix (e.g. serum, urine, and others) consistently detected distinct biomarker signatures with respect to controls and in patients affected by COPD and OSA, specific biomarkers were identified in distinct matrices.⁴

Asthma is certainly linked to airway wall remodelling.⁵ Therefore, the natural matrix (exhaled breath) of the respiratory tract should carry useful biomarkers to monitor changes in the respiratory metabolic phenotype ("metabotype"), therefore becoming a measure of airway inflammation and oxidative stress.⁶ The principle of EBC collection is cooling the exhaled breath, resulting in a fluid sample that contains evaporated and condensed particles derived directly from the airway lining fluid.⁷ EBC is mainly (>99%) formed by water vapour, but also contains aerosol particles in which several biomolecules, including leukotrienes, 8-isoprostane, prostaglandins, hydrogen peroxide, nitric oxide-derived products and hydrogen ions, can be detected.⁷ It is expected that airway surface liquid becomes aerosolized during turbulent airflow; therefore, the condensate reflects the composition of airway surface liquid, although large molecules may not aerosolize. Therefore, it is not surprising that EBC has been used in several metabolomic studies on respiratory pathologies: asthma in children,⁸ adult chronic obstructive pulmonary disease (COPD),⁹ cystic fibrosis (CF)¹⁰ and smoking-related lung diseases.¹¹

Different metabolotypes characterized by different levels of ethanol, methanol, formate, and acetone/acetoin, were clearly defined from EBC samples of COPD and asthmatic patients, confirming the power of EBC as a suitable matrix, for phenotyping respiratory diseases. (unpublished data)

Recently, we characterized the respiratory metabotype of obese asthmatic patients as compared to lean asthmatic patients, indicating that NMR-based metabolomics of EBC efficiently characterizes the respiratory metabolic fingerprint, pinpointing phenotypic differences and suggesting unique pathophysiologic pathways involved in the pathogenesis of asthma.¹²

A step forward should be the integration of metabolomics profiles of non-invasive biofluids (plasma, urine, saliva and EBC) to better define the general metabolic pathways involved in class discrimination. Moreover, the inclusion of more mechanistic parameters, such as cellular and mediator patterns, could clarify cellular sources and disease-specific mechanisms that originated the metabolites and the pathogenetic role of the metabolic pathways in which they are involved, most likely clarifying partially the relationship with clinical parameters.

In conclusion, we suggest that all biological matrices, with no distinction, are helpful to define specific metabolic phenotypes, which separately may contribute a strategy for patient stratification based on unbiased biomarkers, with important diagnostic and therapeutic implications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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