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NMR Metabolomics to Explore Respiratory Disorders

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Abbreviations: BALf: Bronchoalveolar Lavage Fluid; EBC: Exhaled Breath Condensate; ELF: Epithelial Lining Fluid; NMR: Nuclear Magnetic Resonance; MS: Mass Spectrometry; LC: Liquid Chromatography.

Introduction to Metabolomics

Metabolites are the end products of enzymatic activity inside the cells. Being in general characterized by molecular masses less than 1 kDa, they are represented by amino acids, carbohydrates, lipids, hormones, nucleotides and other small molecules. Due to the proximity of metabolites to a phenotype or disease, detecting and quantifying changes in the concentration of metabolites may reveal the range of biochemical effects induced by a disease condition or its therapeutic intervention. This is exactly the task of Metabolomics, the newest 'omics' science whose term was coined in analogy with those of the previously developed Genomics and Proteomics. Metabolomics is not only complementary to the other two approaches but, being able to provide information that allows a better understanding of cellular biology, it looks like the perfect tool suitable to integrate them. In fact, although genomics provides good fingerprints of hereditary information, it should be underlined that not all human diseases are associated with genetic defects. On the other hand, up- or down-regulation in protein(s) expression revealed by proteomics not necessarily correlates with a perturbation in their biological activity. Thus, given that the metabolome reflects changes that occur in the transcriptome, genome, or proteome, it can provide an instantaneous snapshot of cell physiology.

NMR Technology

Given the huge number, the chemical diversity and the dynamic range of metabolite concentration, analyzing their entire range would require the combination of different analytical methods. Nevertheless, very often a single technique is able to provide a good snapshot of the system under investigation. The most used methods applied are currently gas or liquid chromatography (GC or LC) in combination with mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. The peculiarities and advantages of NMR (it is rapid, quantitative, non-destructive and requires minimal sample pre-treatment) makes often this method more attractive than the others for providing a rapid and accurate metabolic picture of the sample. Briefly, the biological sample under investigation is placed in a strong magnetic field to align nuclei (e.g., 1H, 13C, 15N, 31P) contained in the analytes. The interaction of a high power short duration radio frequency pulse leads to the generation of small NMR signals which are translated into peaks that are displayed across a spectrum. In principle, by comparing the position of these signals with reference data present in the literature, NMR resonances of common metabolites can be identified. When dealing with overlapping of signals, the use of a more sophisticated procedure (two-dimensional NMR experiments) that improve resolution is required.

NMR applied to Pulmonary Disorders

The rapid expansion of NMR metabolomics in the field of lung disorders resulted in the publication of a wealth of articles focused on the identification of metabolites associated with different diseases including chronic obstructive pulmonary disease, asthma, cystic fibrosis, tuberculosis, sarcoidosis, invasive pulmonary aspergillosis, pulmonary arterial hypertension, pulmonary langerhans cell hystiocytosis, high altitude pulmonary edema, adult respiratory distress syndrome, bronchiolitis obliterans syndrome, pulmonary emphysema associated with α1-antitrypsin deficiency. In most cases the matrices investigated were those that much better than others reflect the local environment they came from, i.e. bronchoalveolar lavage fluid (BALf), induced sputum, exhaled breath condensate

(EBC), epithelial lining fluid (ELF). It was observed that profiles of patients with different pathological conditions shared largely the same panel of metabolites. However, while appearing similar, the patterns of peaks evidenced distinctive differences in terms of presence/absence of some specific metabolites and prompted investigators at focusing on their quantitative variations. In general, from among the numerous metabolites detected, those that allowed to discriminate patients from healthy controls were identified as Krebs cycle intermediates, mono- and disaccharides, nucleotides, phospholipid precursors, amino acids, alcohols, ketones, short-chain fatty acids. The fact that these molecules were "heterogeneous", other than being a source of confusion, was an incentive to the search of a rationale for reasoning on their potential role in the onset of the disorder. Although belonging to different chemical classes, these analytes contained a piece of information that was unequivocally useful to distinguish profiles of health from those of disease states. In most cases multivariate statistical analyses (i.e. principal component analysis and/or orthogonal partial least squares discriminant analysis) were carried out to confirm that data concerning discrimination between cohorts of subjects under investigation were statistically significant. Application of appropriate platforms to the lists of metabolites also allowed interpretation of acquired data and consequent generation of biochemical pathways aimed at defining their relationships. These studies allowed pointing out a good number of pathways that played a critical role in different lung disorders. These included cellular energy metabolism (alteration in β-oxidation of fatty acids, glycolysis, pentose phosphate pathway), the pyruvate and the taurine/hypotaurine pathways. The fact that a number of metabolites identified in these studies were common to a variety of pulmonary disorders could mean that they were not very specific to a given pathology. However, given the common clinical traits among several lung disorders, this finding was not surprising. Taken together, all NMR experimental data so far generated evidenced/confirmed that some relevant pathways shown to be involved in a lung disorder, most likely were deregulated also in other cognate pulmonary pathologies.

Conclusions

Although the application of NMR to metabolomic studies of respiratory disorders is still in its infancy, the data so far published represent a significant contribution to the identification of biomarkers which may aid in the diagnosis and/or treatment of lung diseases. Metabolome is characterized by a peculiar ability to change very quickly over time. Thus, succeeding in identifying molecules that nobody expected to be there (and the metabolic pathway they are involved in) would be an important contribution which may open the door to clinical studies.

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