Post-Graduate Course: Microbiome and omics in allergy

Metabolomics in Respiratory Diseases

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Metabolomics

The central dogma of molecular biology has been a linear conception of the cell where the general flow of information goes from gene to transcript to protein, however, this traditional thinking is no longer accepted and is represented as dynamic protein complexes interacting with neighboring metabolites[1].

Metabolites are small molecules (< 1000 Da), including peptides, amino acids, nucleic acids, carbohydrates, organic acids, vitamins, polyphenols, alkaloids and inorganic species, and represent the functional phenotype in a cell, tissue or organism[2]. The collection of them is called metabolome and this is chemically transformed during metabolism and served as direct signatures of biochemical activity and are therefore easier to correlate with phenotype. Therefore, metabolomics has become a powerful approach that has been widely adopted for clinical diagnostics[3]. There are two traditional approaches: targeted and untargeted (or global) metabolomics. A targeted approach is usually performed for a defined set of metabolites measurement, and an untargeted approach may be taken in which as many metabolites as possible are measured and compared between samples without bias.

1. Targeted metabolomics

This approach refers to a method in which a specified list of metabolites is measured, typically focusing on one or more related pathways of interest[4]. Targeted metabolomic approaches are commonly driven by a hypothesis that motivates the investigation of a particular pathway. Also, there are many analytical tools available for measuring metabolites (e.g., GC/MS, LC/MS, NMR) and literatures investigating optimal protocols for the sample preparation and analysis of specific classes of metabolites. This approach can be effective for measuring the influence of drugs or genetic modifications on a specific enzyme[5].

2. Untargeted metabolomics

Untargeted metabolomic methods are global in scope and have the aim of simultaneously measuring as many metabolites as possible from biological samples without bias. Untargeted metabolomic experiments are often hypothesis generating rather than hypothesis driven. In contrast to targeted metabolomic results, untargeted metabolomic data sets are exceedingly complex with file sizes on the order of gigabytes per sample and there are deviations in retention time from sample to sample as a consequence of column degradation, sample carryover, small fluctuations in room temperature as well as other variations. Manual inspection of the thousands of peaks detected is impractical and is complicated, and metabolite identification is a time-intensive process. In response to these challenges, introduction of metabolomic software becomes routine[6,7].

Although these complications are existing, an untargeted approach is recognized as a powerful tool for researchers as it has great potential to provide insights into biological processes. Given its sensitivity, high throughput and minimal sample requirements, untargeted metabolomics has broad applicability across a multitude of biomedical inquiries. In particular, it has been useful in identifying altered metabolic pathways in disease that represent novel drug targets[8]. Also, as the field of systems biology has emerged from the combination of global analyses[9], contemporary metabolic profiling experiments are complemented by genomic sequencing and proteomic screening and connected to genotype and phenotype[10-13].

Metabolomics in respiratory diseases

Respiratory diseases are associated with metabolic disturbances in the whole body. Because metabolomics can readily detect subtle changes in metabolic networks, the investigation of metabolite concentrations may provide predictive biomarkers relevant to respiratory disorders and new insights into the biological mechanisms of acute or chronic respiratory diseases. However, compared to metabolic disorders (e.g., obesity, diabetes), a few metabolomic study has examined in respiratory diseases. Respiratory illness is a common problem across the countries. Millions of people suffer from genetic or environmentally developed respiratory conditions. Most often, smoking or infections are to blame. Given the major public health concerns related to respiratory diseases, metabolite biomarker exploration for the prediction and prevention of respiratory diseases is required.

In respiratory diseases, reaching early diagnosis and discrimination of subtypes of these respiratory diseases is quite a challenging task than other chronic illnesses (e.g., asthma). There are metabolomics studies using diverse biological specimens (e.g., urine, blood, exhaled breath condensate, bronchoalveolar lavage fluid, and tissue). Among these, urine and blood are the most commonly used biofluids for metabolomics based studies, as both samples contain thousands of detectable metabolites and can be

obtained via non-invasive and minimally invasive methods, respectively.

1. Asthma

Asthma is characterized by shortness of breath due to reversible airway obstruction and abnormal airway reactivity to various stimuli[14]. Asthma is a heterogeneous syndrome with many clinical classifications based on patient symptoms, lung function and response to therapy. Unfortunately for clinicians, reaching the diagnosis of asthma and its management are more difficult than other chronic illnesses[15,16]. Although accurate invasive airway measurements (e.g., bronchoscopy) are possible, this method remains expensive and also unavailable in routine clinical settings. Thus, research has focused on a simple, non-invasive test for detection of asthmatic patients. For this purpose, investigators used some techniques such as metabolomics.

There have been many efforts to discover biomarkers for diagnosis and discrimination of asthma subtypes such as aspirin-exacerbated respiratory disease (AERD) and aspirin-tolerant asthma (ATA) through untargeted metabolomics. Recently, Park et. al. revealed serum metabolite levels of LTE4 and LTE4/PGF2alpha ratio were identified as potential diagnostic metabolite markers for AERD, which were closely associated with major pathogenetic mechanisms underlying AERD[17]. Especially, those LTE4/PGF2alpha ratios were also well associated with elderly asthmatics as well as peripheral eosinophil counts[18]. Additionally, they found serum sphingosine-1-phosphate and urine sphingosine as potential biomarkers of AERD and addressed that there are metabolic disturbances of sphingolipid metabolism in AERD patients[19].

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