Metabolomic Profiling of Lipids for Biomarker Discovery

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Biomarkers are key molecular or cellular substances that are evaluated as indicators of a biological state. They play an important role in understanding the biological processes, pathogenic processes, and pharmacologic responses. Some of the methods to discover biomarkers in different disease models include enzyme-linked immunosorbent assays (ELISA) [1], biosensors [2,3], gas chromatography/mass spectrometry (GC/MS) [4], liquid chromatography (LC) /MS [5], and LC/MS/MS [6,7]. LC/MS/MS is currently the most powerful tool for metabolomic profiling of biomarker discovery due to its specificity and high sensitivity. Metabolomics is the systematic study of the unique chemical fingerprints of small molecules or metabolite profiles that are related to a variety of cellular metabolic processes in a cell, organ, or organism. Metabolic profiling provides direct and indirect physiologic insights that can potentially be detectable in a wide range of biospecimens. Metabolomic platforms for lipids are important because these signaling molecules regulate many fundamental biological processes. For example, the lipids of the arachidionate cascade, which includes eicosanoids, are the targets of 75% of the world’s pharmaceuticals. This article is focused on the application of metabolomics profiling of lipids and the analytical method for lipids profiling is described elsewhere [8].

Eicosanoids are lipids produced from arachidonic acid including prostaglandins (PGs), epoxyeicosatrienoic acids (EpETrEs), hydroxyeicosatetraenoic acids (HETEs), thromboxanes (TXs), leukotrienes (LTs), and lipoxins (LXs). Among these compounds, EpETrEs are of biological importance from several aspects. EpETrEs are anti-inflammatory, analgesic, cardiovascular protective, and anti-hypertensive [9,10]. EpETrEs can be converted to their less biologically active corresponding vicinal diols, dihydroxyeicosatetraenoic acids (DiHETEs) by a xenobiotic-metabolizing enzyme, soluble epoxide hydrolase (sEH). Inhibition of sEH by either sEH gene knockout or using a selective sEH inhibitor (sEHI) can increase the levels of EpETrEs in vivo and leads to decreased inflammation. sEH has proven to be a therapeutic target for acute inflammation, pain, and cardiovascular diseases [11]. Potent sEHs have been developed for several decades and have emerged as therapeutic drug agent for treating inflammatory diseases. By using metabolomic profiling method, changes of eicosanoid profile could be evaluated and used as valuable biomarkers for assessing the engagement of sEH in vivo [7]. For example, a significantly decreased EpETrEs/DiHETe ratio, which represents an inflammatory state, was found in a murine model of myocardial infarction by lipids metabolomic profiling. However, with the dramatically increased ratios of EpETrEs/DiHETEs after drug treatment, sEHI was demonstrated to be highly effective in the prevention of progressive cardiac remodeling post myocardial infarction [12]. This indicates that the ratios of EpETrEs/DiHETEs are closely related with the function of sEHI. Other studies using lipids metabolic profiling also revealed that either the ratios of EpETrEs/DiHETEs or the increased EpETrEs is correlated with sEHI treatment and may be used as a potential biomarker to evaluate the engagement of sEHI [13-17].

20-hydroxyeicosatetraenoic acid (20-HETE), one of the metabolites from arachidonic acid produced by cytochrome P45s (CYP450s), is another important compound of eicosanoids. It is a potent vasconstrictor and plays an important role in cardiovascular function. In a recent study, 20-HETE was found to be an unexpected biomarker in a selective cyclooxygenase (COX)-2 inhibitor, rofecoxib, mediated cardiovascular events [18]. By metabolomic profiling of the representative oxylipins derived from arachidonic acid and linoleic acid mediated by COXs, CYP450s, and lipoxigenases (LOXs) pathways instead of monitoring arachidonic acid generated oxylipins from COX enzymes only, the authors found a 120-fold increase of 20-HETE after oral administration of rofecoxib for 3 months in a murine model. And this dramatic change is correlated with a significant shorter tail bleeding time which is one of the side effects of rofecoxib. Their work suggested that 20-HETE may potentially be used as a biomarker of rofecoxib induced cardiovascular adverse events.

20-HETE has also emerged as a new biomarker and therapeutic target for hypertension. The vascular actions of 20-HETE are known to be prohypertensive. It is a vasoconstrictor in small arteries and also has natriuretic properties [19]. Sodhi et al. provided evidence that 20-HETE generated by increased endothelial CYP4A2 expression led to increased angiotensin-converting enzyme (ACE) and angiotensin-dependent hypertension [20]. One recent study by Chabova et al. demonstrated that combining 20-HETE inhibition with sEHI inhibition successfully decreased blood pressure and improved kidney function in Ren-2 renin transgenic rats that have angiotensin-dependent hypertension [21]. Using another hypertensive animal model, Zhang et al. recently found that urinary 20-HETE excretion was increased in adrenocorticotrophic hormone (ACTH)-induced hypertensive rats, while inhibition of 20-HETE production by HET0016, a selective inhibitor of 20-HETE, prevented and reversed ACTH-induced hypertension [22]. Taken together, these evidences suggested 20-HETE may be used as a biomarker of vascular dysfunction and as a new therapeutic approach for the treatment of hypertension.

In conclusion, metabolomic profiling of lipids has proven to be a promising tool to gain comprehensive understandings of biological processes. It has played increasingly important roles due to its utility in the identification of candidate biomarkers associated to disease status. Its application has ranged from biological fundamental studies to pharmaceutical research and development, and to clinical research. Biomarker discovery by metabolomic profiling of lipids will have a broad application in the improvement of early diagnostics, patient monitoring and for the evaluation of the safety and efficacy of therapeutic strategies.

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