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Editorial Open Access

Lipidomics: A rapidly Emerging Analytical Platform in Clinical Research

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Lipids have pleiotropic roles in cellular structure and function, serving as metabolic fuels, structural scaffolds, and mediators of signal transduction. Structural lipids are essential scaffolds of membranes (glycerolipids and glycerophospholipids), membrane lipid rafts (plasmalogens), myelin (sulfatides and galactoceramides), mitochondrial membranes (cardiolipins), sperm (seminolipids), lung surfactant (plasmalogens and phosphatidylglycerols), lysosomes (bismonoaylglycerol-phosphates), semilysobisphosphatic acids (Golgi).

Advances in mass spectrometry have dramatically improved the ability to interrogate across the full breadth of the lipidome with improved accuracy and precision. The critical advances have involved the introduction of electrospray ionization (ESI), tandem mass spectrometry (MS/MS), and high resolution mass spectrometry. These analytical methods are essential to investigate the immense structural diversity of lipids.

The insights that are provided by lipidomics studies of diseased or perturbed systems are expanding at a rapid rate. Increasing numbers of lipidomics publications in the fields of neurodegeneration, psychiatry, oncology, metabolic diseases, and infectious diseases are demonstrating the ability of these technology platforms to identify clinical biomarkers. In clinical practice, the variability in the underlying pathology of a disease results in even more variability in signs and symptoms. Biomarkers offer the promise to help resolve this problem by providing: 1) early disease detection (antecedent biomarker), 2) more precise definition of disease and co-morbid conditions (diagnostic biomarker), 3) personalized treatment, and 4) biochemical evaluation of treatment outcomes (prognostic/stratification biomarker). In addition, lipiomics offers great promise to define new molecular targets for treating the underlying molecular pathophysiology rather than treating the phenotypic consequences of disease.

While non-targeted lipidomics platforms are generally utilized in pilot studies, targeted methods are more robust, demonstrate lower levels of variability, and metabolite quantitation is absolute. Furthermore, the use of stable isotope internal standards corrects for a large number of methodological issues which include, extraction efficiency, adsorption losses, transfer losses, derivatization efficiency, metabolite desolvation in LC procedures, matrix effects on metabolite ionization, and shifts in retention time with chromatographic systems. Clear conclusions can be drawn from quantitative data of targeted lipidomics assays and next steps defined. Such approaches have the potential to increase the pace of research in complex programs where targeted lipidomics can dissect out critical pathways involved in the pathogenesis of disease. This approach also provides a path to bridge the gap between non-targeted findings and clinical practice. The mechanics of biomarker studies first involve a non-targeted lipidomics evaluation of a small disease population (pilot/training sample set) followed by a larger targeted lipidomics study to provide quantitative data. The final phase of biomarker validation involves a targeted lipidomics evaluation of a large unbiased population, such that the influence of different confounds (e.g. co-morbid conditions, lifestyle factors) on the proposed biomarker can be evaluated. Lipidomics findings from pilot and small validation sets require validation in larger clinical cohorts with diagnostic uncertainty before any biomarker can be utilized in a clinical setting. These trials are very demanding both for the clinicians conducting the patient evaluations and sample collection as well as for the analytical scientists processing the very large numbers of clinical samples.

The challenges for translating lipidomics findings into clinical practice involve both clinical and analytical issues. First, collaborations are essential to obtain the patient numbers required to define the levels of specificity and sensitivity of proposed biomarkers. The analytical issues are more varied and include the lack of availability of analytical and internal stable isotope standards, sample stability, extraction methods, and the resolution of isobars by chromatographic and/or high resolution mass spectrometry.

In summary, the field of lipidomics is rapidly advancing and will provide new biomarkers for clinical utility within this decade.

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