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Mini-review

Lipidomics: Novel insight into the biochemical mechanism of lipid metabolism and dysregulation-associated disease

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ABSTRACT

The application of lipidomics, after genomics, proteomics and metabolomics, offered largely opportunities to illuminate the entire spectrum of lipidome based on a quantitative or semi-quantitative level in a biological system. When combined with advances in proteomics and metabolomics high-throughput platforms, lipidomics provided the opportunity for analyzing the unique roles of specific lipids in complex cellular processes. Abnormal lipid metabolism was demonstrated to be greatly implicated in many human lifestyle-related diseases. In this review, we focused on lipidomic applications in brain injury disease, cancer, metabolic disease, cardiovascular disease, respiratory disease and infectious disease to discover disease biomarkers and illustrate biochemical metabolic pathways. We also discussed the analytical techniques, future perspectives and potential problems of lipidomic applications. The application of lipidomics in disease biomarker discovery provides the opportunity for gaining novel insights into biochemical mechanism.

Contents

Abbreviations: AA, arachidonic acid; AD, Alzheimer's disease; CE, capillary electrophoresis; DHA, docosahexanoic acid; DPA, docosapentaenoic acid; ESI, electrospray ionization; FTICR, Fourier transform ion cyclotron resonance; GC, gas chromatography; GP, glycerophospholipids; HPLC, High performance liquid chromatography; IM, ion mobility; IMS, imaging mass spectrometry; LC, liquid chromatography; LysoPC, lysophosphatidylcholine; MALDI, matrix-assisted laser desorption and ionization; MS, mass spectrometry; MS^{E}, mass spectrometry$^{Elevated\ Energy}$; MUFA, monounsaturated fatty acids; NMR, Nuclear magnetic resonance; PA, phosphatidic acids; PC, phosphatidylcholine; PD, Parkinson's disease; PE, phosphatidylethanolamine; PG, phosphatidylglycerols; PI, phosphatidylinositols; PS, phosphatidylserine; PUFA, polyunsaturated fatty acids; QTOF/MS, quadrupole time-of-flight mass spectrometry; SFC, supercritical fluid chromatography; SM, sphingomyelin; SM, sphingomyelin; TG, triglycerides; TLC, thin-layer chromatography; TOF/MS, time-of-flight mass spectrometry; UHPLC, ultra-high performance liquid chromatography.

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1. Introduction

Lipidomics is a branch of the field of metabolomics. Lipidomics was first introduced by Han and Gross in 2003 after genomics and proteomics [1]. Lipidomics was the qualitative and quantitative analyses of the lipid components from serum, plasma, tissue, whole organism or cell. Lipidomics focused on the comprehensive identification and quantification of all lipids and the characterization of their interactions with other lipids and proteins as well as protein expression associated with lipid metabolism and function, gene regulation in response to a stimulation or disturbance [2]. Lipidomics has rapidly progressed and is being used to address questions in biological systems. Lipidomics has gained application widely in cellular signaling networks to discover and illuminate biochemical mechanism. The National Institute of General Medicine-supported LIPID MAPS (pathways strategy and lipid metabolites) has been the reorganization of lipid classification to facilitate bioinformatic organization and making databases more compatible with search functions [3]. Recently, one review has reported the structural organization of the lipidomics database and online tools provided in the LIPID MAPS consortium [4]. This included comprehensive and systematic discussion of the different problems associated with structural representation, nomenclature and classification of lipid molecules that were considered in the structural identification and biological pathway analysis from database.

Lipids were a heterogeneous category of compounds from cellular metabolites. Differing from other biological molecules, lipids did not have a certain individual chemical structure. The LIPID MAPS database defined lipids as hydrophobic or amphipathic compounds that were found from two main different biosynthetic pathways. Acyl carrier protein intermediates were condensated from acyl-CoA and malonyl-CoA esters and the intermediacy of a carbanion structure including fatty acids, glycerolipids and phospholipids. The second pathways were the carbocation biosynthetic pathway associated with branched chain 5-C pyrophosphate intermediate condensation including polyisoprenoids and steroids [5]. Based on the chemical structure diversity and biosynthetic pathways, lipids have been divided into 8 categories: fatty acyls, glycerolipids, glycerophospholipids (GP), sphingolipids, sterol lipids, prenol lipids, saccharolipids and polyketides [3]. Each category lipid was further divided into subcategory based on metabolic pathways. The eight functional divisions of lipid categories were shown in Table 1. Most of these lipids not only were directly associated with the biochemical process, but also were regarded as disease biomarkers for disease diagnosis, disease prognosis and pharmaceutical discovery and therapeutic effects. This review will discuss the popularly and widely technological advances including mass spectrometry (MS)-based shotgun lipidomics and MS coupled with separation techniques-based lipidomics in the field of lipid characterization, followed by an overview of how these technological advances can be applied to discovery disease biomarker to reveal the role of lipids in cellular functions and various disease pathologies including brain injury disease, cancer, metabolic disease, cardiovascular disease, respiratory disease and infectious disease. This review will also discuss the challenges facing lipidomics research.

2. Analytical technology in lipidomics

Lipidomics was applicable to the fields of various disease diagnosis and drug therapy, such as neuropsychiatric disease, cancer, metabolic syndrome, cardiovascular disease, inflammatory disease and infectious disease. Currently, the analytical techniques are applied to various biological samples including blood, plasma, serum, urine, cerebrospinal fluid and cultured cells as well as all types of tissue from animal models or clinical patients.

Based on the diversity of lipid compositions, lipidomics came up with a serious challenge in the field of analytical chemistry. Nuclear magnetic resonance (NMR), MS and other techniques became powerful tools for lipid structure identification. Direct-infusion MS and NMR techniques did not need sample pre-separation and made it less time-consuming and they provided potential for lipid structure characterization with high throughput and high sensitivity. However, without sample pre-separation before MS and NMR detection, Direct-infusion MS and NMR had some difficulties in indentifying various lipid structures. Thus, different chromatographic separation technologies coupled with MS were widely accepted for lipidomic analysis owing to high throughput and high sensitivity [6]. With the rapidly development of different separation techniques, thin-layer chromatography (TLC), gas chromatography (GC), liquid chromatography (LC), capillary electrophoresis (CE) and supercritical fluid chromatography (SFC) became mainly tools for lipidomic studies [7–10]. Coupled with different types of MS, different separation techniques could provide comprehensive and systematic information of structural identification on almost all lipids in biological samples, while chromatographic separation may cost more time and solvents than direct-infusion MS or NMR. In addition, imaging mass spectrometry (IMS) and spectroscopy techniques were suitable for study of biological dynamic processes revealed real-time analysis *in vivo*.

2.1. Shotgun lipidomics

Traditionally, the analyses of lipids have relied on analytical techniques with low sensitivity and resolution, such as TLC where lipid analysis was limited to the study of entire lipid classes. But this method was relative simple and low experimental costs and it was still common used in many studies. With the development of GC, GC was available for the different fatty acid separation in simple mixtures [11]. However, the individual lipids of identification and quantification remained challenging in crude extract. The field was advanced when GC coupled with MS. In past ten years, lipid research has made great progress by rapid advances in MS, especially soft ionization techniques including matrix-assisted laser desorption and ionization (MALDI) and electrospray ionization (ESI). With the advances of MS, they provided certain possible for determining the entire lipidome. The m/z data provided additional structure information from MS/MS detection in which lipid molecules were fragmented via collision induced dissociation. ESI source was usually employed in lipidomic study although other ionization techniques including atmospheric pressure ionization and MALDI have also been used in lipidomics. ESI source can provide a more detailed structure information, such as the indication position of