

Review Article

Lipidomics: A Promising area in "OMICS" Research

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Abstract

Lipidomics is defined as the analysis of lipids on the systems-level scale together with their interacting factors. In this review, we will discuss the technical developments in the field of lipidomics and overview the current state of the lipid bioinformatics field as well as suggest few potential new areas of research. The role of bioinformatics in the development of lipidomics will also be discussed.

Keywords: Lipidome; Metabolomics; Genetic disorder; Environmental; Triggers; Disorders

Introduction

The word "lipidome" first appeared in the literature in 2001. Lipidomics is an emerging field of biomedical research which includes complex lipidome analysis. Basically, a lipidome is the comprehensive and quantitative description of a set of lipid species present in an organism. Lipidomics involves systems-level identification and quantitation of thousands of pathways and networks of cellular lipids molecular species and their interactions with other lipids, proteins and other moieties in vivo [1]. Lipids are small molecules that share common physical and chemical properties as a class, whose presence and abundance are key to much of metabolic regulation, from subcellular compartments to whole body energy control and signaling. It is an emerging field in biomedical research. It aims at systems scale detection, characterization and quantification of lipids. Within metabolomics, lipidomics has its own identity [2]. At the level of the cell, lipidomics must quantitatively describe all lipids and their functions. Lipidomics, integrated with genomics, proteomics, and metabolomics (Figure 1) will contribute toward understanding how lipids function in a biological system and will provide a powerful tool for elucidating the mechanism of lipid-based disease, for biomarker screening, and for monitoring pharmacologic therapy (Figure 2) [3].

Lipids: The essential metabolites

Lipids are amphipathic small molecules which include fats, waxes, sterols, fat-soluble vitamins, monoglycerides, diglycerides and phospholipids. The crucial role of lipids in a cell, tissue and organ physiology is evident by their unique membrane organizing properties that provide cells with functionally distinct subcellular membrane compartments. The molecular nature of individual entities of glycome and lipidome such as the carbohydrates and lipids is highly complex due to their diversity and perpetual metabolic flux in a biological system at either microsystem or macrosystem levels [4].

The main biological functions of lipids include:

- 1. Energy storage and structural components of cellular membranes.
- 2. Cell signaling
- 3. Endocrine actions
- 4. Essential role in signal transduction, membrane trafficking and morphogenesis.

The crucial role of lipids is demonstrated by a large number

of genetic studies and by many human diseases that involve the disruption of lipid metabolic enzymes and pathways [5]. Examples of such diseases include cancer, diabetes, as well as neurodegenerative and infectious diseases. So far, the explosion of information in the fields of genomics and proteomics has not been matched by a corresponding advancement of knowledge in the field of lipids, which is largely due to the complexity of lipids and the lack of powerful tools for their analysis. Novel analytical approaches in particular, liquid chromatography and mass spectrometry for systems-level analysis of lipids and their interacting partners now make this field a promising area of biomedical research, with a variety of applications in drug and biomarker development [6,7].



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Novel tools for lipid research [8]

- Structure-drawing tools
- MS prediction tools

Technical Developments of Lipidomics

Lipidomics mass spectrometry

Mass spectrometry has emerged as a powerful tool for the analysis of all lipids.For a long time, MS was restricted to analysing small and volatile lipids. In the late 1980s, two 'softa' ionization techniques were developed for generating ions of intact biomolecules electrospray ionization (ESI) and matrix assisted laser desorption/ionization (MALDI). These two techniques allow high mass and nonvolatile compounds such as intact lipids to be amenable to mass spectrometric analyses. ESI produces gas-phase ions from molecules in a solution, and is easily directly coupled to liquid chromatography. This technique is currently the most frequently used in lipidomic research. Ion trap mass spectrometers, however, have several disadvantages for lipidomics research. The triple quadrupole mass spectrometer has been the work-horse for studying small molecules mainly because of its high performance for quantitation, its ability to perform precursor ion scans and neutral loss scans and its exquisite sensitivity for identifying specific small molecules. Its characteristics are well suited for lipid analysis. MALDI-TOF MS has become a very promising approach for lipidomics studies, particularly for the imaging of lipids from tissue slides. Imaging mass spectrometry of lipids in tissues has opened new insights into the distribution of lipid molecular species with promising application to study pathophysiological events and diseases [9]. The polymerase chain reaction (PCR) is an enzymatic reaction which follows simple, predictable and well understood principles. Selective amplification of nucleic acid molecules, that are initially present in

minute quantities, provides a powerful tool for analyzing nucleic acids [10]. Several Omics methods have been applied to identify virulence genes, i.e., DNA microarrays, In Vivo Expression Technology (IVET), Signature-Tagged Mutagenesis (STM), Differential Fluorescence Induction (DFI) etc [11,12].Comparative analysis of lipid profiles, which stem from two physiologically linked conditions is particularly powerful for applications in drug and biomarker development. First, it leads to the identification of pathways related to lipid metabolism. Second, multiparameter lipid biomarkers will provide better diagnostics in preclinical trials using model organisms and in clinical presentations in humans [13,14]. The relative rates of development of the high throughput computational methods for the detection of SNPs (Single Nucleotide Polymorphism) and small indels (insertion/deletion) has gained wide applications in the field of the molecular markers [15]. It has been recently established a highly sensitive MS for both glycans and glycopeptides by pyrene derivatization [16]. Efforts have been made to prioritize positional candidate genes for complex diseases utilize the protein-protein interaction (PPI) information. But such an approach is often considered too general to be practically useful for specific diseases [17,18].

Mass spectrometry based lipid analysis

Many modern technologies (including mass spectrometry (MS), nuclear magnetic resonance (NMR), fluorescence spectroscopy, column chromatography, and microfluidic devices) [19] are now being used in lipidomics to identify, quantify, and understand the structure and function of lipids in biological systems.

Improvements in mass spectrometric technology have proved highly efficient for the characterization and quantification of molecular lipid species in total lipid extracts. The main advantage of mass spectrometry is its ability to separate and characterize charged ionized analytes according to their mass-to-charge ratios (m/z). It can also provide structural information by fragmenting the lipid ions by collision-induced dissociation (CID). The various techniques used to record these fragmentation reactions are called tandem MS or MSn [20]. These attributes lead to unparalleled selectivity, sensitivity and the ability to provide structural information for components in complex mixtures. Lipidomics is developing as an independent discipline at the interface of lipid biology, technology and medicine. Technological advancements, most notably in liquid chromatography and mass spectrometry, allow sensitive and highly selective analysis of lipids with diverse chemical composition and in complex mixtures [21].

The developed MS techniques can be mainly categorized into three groups:

Global Lipidomic analysis: Identify and quantify hundreds to thousands of cellular lipid species via a high throughput basis. Different shotgun lipidomics-based platforms have been developed and extensively used to analyze diverse pathways and networks associated with lipid metabolism, trafficking, and homeostasis. Newly emerging mapping techniques play major roles in studying the spatial and temporal relationships of lipids.

Targeted Lipidomics Analysis: Identification of one or a few lipid classes of interest. LC-MS and LC-MS/MS based methods have been extensively utilized for this purpose.

Novel Lipid Discovery: Directed towards the discovery of novel lipid classes and molecular species. Methodology using LC coupled

with MS plays an essential role in this area through different enrichment technologies.

Imaging MS by MALDI-TOF in lipidomics

MALDI-TOF MS has become a very promising approach for lipidomics studies, particularly for the imaging of lipids from tissue slides. Interestingly, such MALDI-TOF approaches have been used in lipidomics to investigate the spatial distribution of the levels of lipid species in tissue samples. Methods to couple MALDI-TOF MS and thin-layer chromatography (TLC) for lipid analysis were developed by several research groups. We expect that MALDI imaging will be an increasingly important tool for studying the lipidome in view of its ability for rapid screening of lipid distributions in tissue slides [22].

Identification of phospholipids by ESI-MS/MS

Lipidomics also has its own peculiarities. Phospholipids are sensitive to oxidation, light and enzymes such as lipases. Phospholipids moved with different metal ions normally generate different fragmentation patterns from one another. The complementary structural information obtained through ionization via metal ion adduction, especially structural information on the two acyl constituents, could be used to uncertainly identify the lipid species of interest. Although the field of lipidomics is dominated by MS, other techniques have also been introduced. Nuclear magnetic resonance (NMR) to analyse lipid profiles of human erythrocytes. A simple method for separation and quantification of neutral lipids was developed using thin-layer chromatography (TLC) and high-performance fluorescent scanning [23].

Lipid Biomarkers in Chronic Disease

A major challenge facing healthcare providers is the growing epidemic of obesity and metabolic syndrome and associated increases in diabetes and heart disease [24,25]. These complex diseases are influenced by many factors, including genetics, diet and lifestyle. Dyslipidemia is a major feature, usually preceding the clinical onset of disease. One of the most widely used lipid biomarkers has been cholesterol [26,27] which, in the form of total blood cholesterol and/ or high density lipoprotein (HDL) cholesterol, has been used in risk calculations for heart disease for over 50 years. Triglycerides are also used clinically for risk assessment of heart disease and diabetes [28, 29]. As we move into the lipidomics era, the potential to accurately and rapidly measure hundreds of individual lipid species provides the opportunity to use more complex lipid profiles as biomarkers of chronic disease. Importantly, many of the risk factors contributing to disease are likely to also influence lipid metabolism and consequently will be reflected in the lipid profile of an individual. The challenge for researchers will be to characterize the profiles that best reflect disease status or risk and translate those into clinically relevant tools. It is becoming increasingly evident that many neurological disorders, such as bipolar disorders, schizophrenia and neurodegenerative diseases, involve de-regulated lipid metabolism [30]. Aberrant cholesterol metabolism is linked to Alzheimer's disease. Aggregates of β-amyloid protein on membrane surfaces and peptide aggregation are promoted by interaction with GANGLIOSIDES. Synucleins, a family of small neuronal proteins of unknown function, bind to fatty acids and lipids and regulate their oligomerization. Mutations in α -synuclein are associated with rare familial cases of early-onset Parkinson's disease. More recently, mutations in the gene encoding glucocerebrosidase were shown to be a susceptibility factor for Parkinson's disease. Niemann-

Pick disease type C (NPC) is a lysosomal storage disease (LSD) and cholesterol, glycosphingolipids and sphingosine are dysregulated in NPC mouse models and in the brains of human patients. Lipidomic approaches are also emerging as suitable diagnostic tools for certain diseases in humans such as myocardial lipidomics and neurolipidomics. Thus, systems biology-centered lipidomics appears as a promising analytical platform in preventing or treating several lipidome-based disorders/diseases [31]. Lipidomics approach has provided insights and alternatives into understanding the complexity of biochemical events that occur in ischemia and the role of NAE as protectants [32]. Hydropericardium syndrome is an important emerging disease of domestic fowl caused by fowl adenovirus serotype 4 (FAV-4) with high mortality rate causing heavy economic loss to the poultry industry [33]. Ion imaging technology of glycosphingolipids molecular species could provide valuable information for metabolic changes of lipids in diseases and aging and furthermore, opens a gate for a new lipidomics with molecular imaging [34]. Assessing glycosylation on whole bacteria using lectin arrays may not reflect bacterial glycosylation, but interactions between bacteria and the glycosylation present on lectins. Clinically important bacterial strains are capable of inducing severe autoimmune responses may aid in prevention and/or early diagnosis of debilitating post infection conditions [35]. Oryza sativa (japonica cultivar-group) species is an important cereal and model monocot. It has generated a matrix frequency for genetic code analysis, which helps in the study of complete genome residues [36]. The l₁ least square classifier may become a promising automatic cancer diagnosis tool by consistently distinguishing gene profile classes. Those genes with great absolute regression coefficients may serve as biological marker candidates for further investigation [37,38]. Damage analysis in metabolic pathways is one of the most highlighted fields in systems biology area. Damages in metabolic pathways can be identified by representing the metabolic pathway in the form of graphs. The detection of these damages can help understand the disorders caused due to these damages [39]. Development of S. mutans as a biofilm over tooth surfaces by suppressing mucosal immune barrier provides a basis for future drug development and new approach in prevention and treatment of dental caries [40].

However, in context of high-throughput lipidomic profiling and systems biology studies, the currently available online resources face threefold challenge: [41]

- 1. Due to high volumes of information available from highthroughput lipidomics experiments, the database system has to be efficiently linked to the analytical platform generating the lipid profile data, as well as to chemo- and bioinformatics system for compound identification and linking the information to other levels of biological organization to enable systems approaches [42].
- 2. Due to diversity of lipids across different organisms, tissues, and cell types, it is unlikely any one database can cover all possible lipids. A mechanism is therefore necessary that facilitates identification as well as discovery of new lipid species in biological systems from available data [43].
- 3. Currently available pathway-level representation of lipids in databases such as KEGG is limited to pathway representation of generic lipid classes, i.e. including mainly the head group information, and not including the fatty acid side chain information. Therefore, these lipid databases lack the level

of detail that is becoming available by modern LC/MS based approaches [44]. A microarray image processing and data analysis package *Matarray*, where quality scores are defined for every spot that reflect the reliability and variability of the data acquired from each spot [45-47].

Lipidomics and Bioinformatics

Lipid bioinformatics is an emerging need as well as challenge for lipid research [48]. Lipid concentration changes in biological systems reflect regulation at multiple spatial and dynamic scales, e.g., biochemical reactions in the cells, intercellular lipid trafficking, changes in cell membrane composition, systemic lipid metabolism or lipid oxidation. Central goal of Bioinformatics is recognized as the major area of research to determining protein functions from their genomic sequences and to develop personalized medicine [49-51]. Bioinformatics is being used to get the design in silico of hsp65 (heat shock protein) molecule. Hsp65 is a Mycobacterium leprae chaperone whose gene has been efficiently used as experimental DNA vaccine against tuberculosis and clinical trial against tumor [52-54]. There are Computational systems biotechnology which has made a platform to experimental techniques for producing commodities with a low cost, good quality and quantity, and fastens the fermentation processes in industry [55,56]. Computational prediction of discontinuous B-cell epitopes remains challenging, but it is an important task in vaccine design [57]. Function annotation of genes and proteins were carried out by using databases like SMART, Interproscan, Pfam, JAFA, COG, and BLAST. Among 114 conserved hypothetical proteins only 35 proteins have been annotated [58].

There is a bioinformatics strategy for lipidomics analysis. It has been utilized the recently developed nomenclature of lipids to generate a diverse scaffold of lipid compounds represented by the Simplified Molecular Input Line Entry System (SMILES) representation each compound entry is linked to the available information on lipid pathways and contains the information that can be utilized for automated identification from high-throughput LC/MS-based lipidomics experiments [59,60]. It has investigated the changes of correlation structure of the lipidome using multivariate analysis, as well as reconstruct the pathways for specific molecular instances of interest using available lipidomic and gene expression data [61,62]. The four essential molecular building blocks of cells are proteins, nucleic acids, lipids and carbohydrates are often referred to as glycans. Nucleotide and protein sequences are very important for all bioinformatics applications and research, whereas glycan and lipid structures have been widely neglected in bioinformatics [63].Viral Microsatellite Database (VMD) is a database currently hosts microsatellites of around 3500 viral genomes along with their alignments, locus information, imperfection info, protein info etc [64].

Challenges for Lipidomics

Due to its specificity and complexity, lipidomics research is quite challenging, exciting, and unique. As opposed to genomics and proteomics, there is no information that can predict the number of individual lipid molecules present in an organism. Current technologies are therefore still unable to map lipidomes.

Moreover, the structural identification of lipids by mass spectrometry is complicated due to diverse lipid classes and lipid molecular species. It also becomes impossible to accommodate all lipid classes with a common method for extraction, chromatography and detection.

Lipid Profile leads to the identification of pathways related to lipid metabolism. Multiparameter lipid biomarkers will provide better diagnostics in preclinical trials using model organisms and in clinical presentations in humans. The crucial role of lipids in cell, tissue and organ physiology is demonstrated by a large number of genetic studies and by many human diseases that involve the disruption of lipid metabolic enzymes and pathways. Examples of such diseases include cancer, diabetes, as well as neurodegenerative and infectious diseases [65].

Conclusions

- 1. Lipidomics, a sub-set of metabolomics, is nascent but has already shown promising discoveries. The genetic equidistance result is the most remarkable result of molecular evolution since it was completely unexpected from classical Neo-Darwinian evolution theory [66]. Lipid research has benefited from a number of recent developments and achievemenGenetic and cell biological research has provided new insights into molecular mechanisms of lipid action.
- 2. It is clear that deregulated lipid metabolism is important in many human diseases, in addition to obvious indications such as diabetes.
- 3. Novel analytical approaches that enable the analysis of lipids in complex mixtures and at a systems level (mainly based on liquid chromatography and mass spectrometry) are being developed at a very rapid pace. Last, these developments in methodology are supported by the more widespread availability of reagents and tools (such as synthetic lipid standards, analogues of natural lipids, lipid affinity probes and so on), which enables the study of lipid metabolism in living cells and in biochemical assays *in vitro*. Lipidomics therefore adds an additional layer of information to data from proteomics and genomics, which will open new opportunities in particular at the various stages in the preclinical and early clinical categories.

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