Gene 554 (2015) 131–139

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

Lipidomics in the study of lipid metabolism: Current perspectives in the omic sciences

Ana Emília Holanda Rolim [a], Ricardo Henrique-Araújo [a], Eduardo Gomes Ferraz [a], Fátima Karoline de Araújo Alves Dultra [a], Luzimar Gonzaga Fernandez [b,*]

[a] Post-graduation Program in Interactive Processes of Organs and Systems, Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil
[b] Institute of Health Sciences-ICS, Federal University of Bahia-UFBA, Department of Biofunção, Laboratory of Biochemistry, Biotechnology and Bioproducts-LBBB, Salvador, Bahia, Brazil

ARTICLE INFO

Article history:
Received 23 August 2013
Received in revised form 14 October 2014
Accepted 23 October 2014
Available online 24 October 2014

Keywords:
Metabolomics
Lipids
Pharmacolipidomics

ABSTRACT

The advances in systems biology and in the development of new technological tools in analysis, as well as in the omic sciences, among which, metabolomics, and more specifically, lipidomics, have made it possible to investigate the structural and functional complexity of lipids in biological systems. Liquid chromatography and mass spectrometry are the analytical approaches most used in lipid research. Biomedical research, with the development of specific markers for lipids, together with new software development, have both enabled the early diagnosis of several illnesses, besides the evaluation of drug activity and treatment efficacy.

1. Introduction

Lipids are metabolites that play an important role in different metabolic pathways. They are structural components of the cellular membranes, in which protein complexes, such as ion channels, receptors, and scaffolding complexes, are embedded (Barrera et al., 2013), whether as a substratum, a product, or as a co-factor of biochemical reactions within a cell.

The analyses of these metabolites are important in order to obtain more data that will integrate cellular function at a molecular level, and in this way, define the phenotype of each cell, or tissue, in response to environmental or genetic modifications. Therefore, the lipid level is fundamental to define the genic function (van Meer, 2005; Villas-Boas and Gombert, 2006).

As lipids take part in several biochemical reactions, integrating different metabolic pathways, any alteration in the said lipids will affect the other metabolites that are directly or indirectly connected. This allows the cell, or the tissue metabolome, to respond quickly to any environmental or genetic modification (Villas-Boas and Gombert, 2006).

The objective of the present article is to review the main concepts of lipidomics, thus putting into context the metabolism of lipids and their importance in the understanding of present-day pathologies and therapies. Besides this, current technologies will be addressed in the analytical methods, as well as in the bioinformation, which make it possible to investigate lipids.

2. Lipids — classification and metabolism

Lipids are a heterogeneous group of water-insoluble compounds, due to their hydrophobic characteristics. The International Lipid Classification and the Nomenclature Committee, together with the Lipids Metabolites and Pathways Strategy (LIPID MAPS) Consortium, defined eight categories of lipids and divided them into classes and subclasses (Fahy et al., 2005; Fahy et al., 2009; Harkewicz and Dennis, 2011). They classified the lipids by their chemically functional backbones and biochemical principles in (1) fatty acyls (FA): fatty acids and conjugates, octadecanoids, eicosanoids, docosanoides, and fatty alcohols; (2) glycerolipids (GL): monoradylglycerols, diradylglycerols and triradyglycerols; (3) glycerophospholipids (GP): glycerophosphocholines, glycerophosphoglycerols, glycerophosphoethanolamines, glycerophosphoglycerophosphates, glycerophosphoserines, and glycerophosphoinositols; (4) sphingolipids (SP): sphingoid bases, ceramides, phosphosphingolipids, neutral glycosphingolipids and acidic glycosphingolipids; (5) sterol lipids (ST): sterols; (6) prenol lipids (PR): isoprenoids; (7) saccharolipids (SL): acrylaminosugars and

Abbreviations: BAD, bipolar affective disorder; CE, capillary electrophoresis; CETP, cholesterol ester transfer protein; MS, mass spectrometry; CNS, central nervous system; DHA, docosahexaenoic acid; ESI, electrospray ionisation techniques; GABA, neurotransmitter gamma-aminobutyric acid; GC, gas chromatography; HDL, high-density lipoprotein; LC, liquid chromatography; LDL, low-density lipoprotein; LXR, liver X receptor; NMR, nuclear magnetic resonance; PI, phosphatidylinositol; PPARs, peroxisome proliferator-activated receptors; VEGF, vascular endothelial growth factor; VLDL, very low density lipoprotein.

* Corresponding author at: Laboratory of Biochemistry, Biotechnology and Bioproducts —LBBB, Institute of Health Sciences, Federal University of Bahia—UFBA, Av. Reitor Miguel Calmon, s/n, Vale do Canela, CEP: 40160-100 Salvador, Bahia, Brazil.
E-mail addresses: luzimargonzaga@gmail.com, luzimar@ufba.br (L.G. Fernandez).

http://dx.doi.org/10.1016/j.gene.2014.10.039
0378-1119/

(8) polyketides (PK): linear polyketides (Harkewicz and Dennis, 2011; Brügger, 2014).

The unique identification number of a lipid can supply information, such as the data source, the category, the class, the subclass, and specific numbers for the lipids. The system allows for the storage and processing of information in different biological units (Fahy et al., 2005; Fahy et al., 2009; Yetukuri et al., 2008; Harkewicz and Dennis, 2011). The structure of some examples of lipids in these eight categories is represented in Fig. 1.

Fatty acids may be saturated, monounsaturated or polyunsaturated. In animals, the residues of predominant fatty acids are the ones with a 16 or 18 carbon atom chain — the palmitic and the stearic acids, which are saturated; oleic acid ($C18\Delta^{9}$) and linoleic acid ($C18\Delta^{9.12}$), which are unsaturated. The linolenic ($C18\Delta^{9.12,15}$) and linoleic acids form arachidonic, eicosapentaenoic and docosahexaenoic acids and are essential fatty acids. The triacylglycerols are the most important way to store energy in the organism, consisting of deposits in the adipose and muscle tissues.

Lipids are not only energy depots and structure builders in the cell, they also play active roles in membrane functions, and can act as messenger molecules. Phospholipids have, among others, the function of forming the double layer that is the basic structure of cell membranes. The polyunsaturated fatty acids are constituents of a large variety of phospholipids, and provide several important properties such as the fluidity and the flexibility of cellular membranes (Harkewicz and Dennis, 2011).

Lipids in membranes do not possess the kind of structure and order which is so characteristic of nucleic acids (DNA and RNA) and proteins; rather lipids display a substantial degree of disorder under physiological conditions and there are no simple structure–function relationships known, as there are in the case of e.g. proteins. Lipids organise themselves in subtle macromolecular aggregates, like the lipid bilayer component of cell membranes, by virtue of physical and thermodynamic driving forces, rather than by the covalent bonding that keeps amino acids together in polypeptides (proteins), sugars in polysaccharides (carbohydrates), and nucleotides in nucleic acids (poly-nucleotides): lipids do not normally form polymers among themselves, and there is no such thing as poly-lipids in biological systems (Mouritsen, 2005, 2011).

Lipids are important molecules for the body's metabolism as a whole, and they also carry out several functions in the organism. The molecular species of the most important plasma lipids, from a physiologic and clinical perspective, are the fatty acids, triacylglycerols, phospholipids, and cholesterol (Santana, 2008). They are transported in the bloodstream as molecular macroaggregated organised structures, called lipoproteins (Henry, 1999; Fahy et al., 2005). Lipoproteins are made up of a hydrophobic lipid core, mainly consisting of cholesterol esters and triacylglycerols, surrounded by a hydrophilic single layer made up of phospholipids, cholesterol, and proteins (Eisenberg and Levy, 1995; Lee et al., 2003).

Lipid transportation in blood circulation can be conceptually divided into two main channels: exogenous, which corresponds to the channel carrying lipids that come from one's diet, and the endogenous, which corresponds to the channel carrying lipids originating in the liver. Besides these, there is also the reversed transportation of cholesterol, which corresponds to the transportation of cholesterol from the extrahepatic tissue to the liver (Brown et al., 1981; Lee et al., 2003).

In the digestion process, enterocytes start the production of particles of nascent chylomicrons. Triacylglycerols, phospholipids, cholesterol ester, and apolipoprotein B-48, are constituents of chylomicrons. These perform the transportation of re-esterified triglycerides into the enterocyte, from a mixture of fatty acids and monoglycerides, produced from triacylglycerol when the diet is hydrolysed by the enzyme lipase. After being synthesised, these are secreted into the lymphatic system (Hussain, 2000). During hepatic capitation, the chylomicron remnant is broken down and releases fatty acids, glycerol, amino acids, and cholesterol, which can be used to produce biliary acids stored in the bile, to make up membranes, or to integrate with the lipoproteins produced and secreted by hepatocytes (Havel and Hamilton, 2004).

The endogenous transportation begins in the liver through the production of a very low density lipoprotein (VLDL), mediated by hormonal factors and other factors that are dependent on the energetic and metabolic balance. After being secreted into the bloodstream, VLDL makes contact with other lipoproteins, by way of collisions, mainly with HDL (Havel and Hamilton, 2004).

3. Concepts and lipidomic study fields

The diversity of lipid structures and their characteristics allows these compounds to perform many biological functions. However, this same complexity sets forth many challenges to characterise, identify, and to quantify this diverse class of molecules (Meikle et al., 2009; Yetukuri et al., 2008).

The arrival of omic science has been a stimulus to determine the concept of a molecular profile in biological systems (Seppänen-Laakso and Oresic, 2009), and the effort aimed at encouraging scientists to explore the lipid field within biological systems has been constant (Rapaka, 2005). Even with the development of the above-mentioned omic science, with its technical strategies, the study of metabolomics, especially lipidomics, is still under-developed (German et al., 2007). This fact is regrettable, because of the importance of lipids in maintaining homeostasis, as well as in the physiopathology of several diseases, including those with high prevalence rates in the population, such as diabetes mellitus, arteriosclerosis, as well as the diseases of greater severity, such as schizophrenia, Alzheimer's disease and cancer (van Meer, 2005; Oresic et al., 2008). This correlation between lipids and the variations that occur in pathological states (as well as in physiological ones), and the respective exogenous influences that act upon them, are based on the fact that these variations are reflected on metabolism (German et al., 2007). Also, understanding the complex system of lipids in biological systems (along with advances in the areas of genomics, metabolomics and proteomics) will allow a better comprehension of the mechanisms of drug activity, and the consequences of psychoactive substance abuse, as well as providing the necessary knowledge for the development of new pharmaceuticals (Rapaka, 2005; Beh et al., 2012).

Metabolomics is an area of study aimed at the overall study of metabolites, as well as several aspects that are related, such as dynamics, composition, interactions, and answers to interventions that occur in their environment (cell, tissue or biofluid) (Oresic, 2009). Lipidomics is considered to be a branch of metabolomics, to which it is very closely related (Oresic, 2009; Navas-Iglesias et al., 2009). Despite this, lipidomics is a distinct discipline for lipids, the study object, the present uniqueness, and the functional specifications, when compared to other metabolites (Han, 2009).

In 2001, Kishimoto et al. (2001) used the term lipidomics for the first time. In 2003, Han and Gross set the limits for lipidomics, and henceforth, the definitions for this discipline were established, and are now related to the integration of the chemical properties inherent to lipids (Han and Gross, 2003; Han, 2009). Within this context, lipidomics is currently considered to be a study of the whole range of lipids (lipidoma), and of the molecules they interact with (proteins, carbohydrates, etc.), seeking, in the same way, to understand the roles that lipids play on biological systems. Within the study field of lipidomics, is the study of how lipids influence membrane architecture, the modulation of transcription and translation, and answers to environmental change due to physiological processes, and in response to diets, drugs, toxins, and genetics. Thus, lipidomic advances in research, on lipids that correlate metabolites and/or lipid metabolic pathways, with the state of metabolic health, are also in studies that narrow down the relations between changes in the regulation of lipid metabolism and pathologic processes (Navas-Iglesias et al., 2009).