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Review

Lipidomics: Practical aspects and applications

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Abstract

Lipidomics is the characterization of the molecular species of lipids in biological samples. The polar lipids that comprise the bilayer matrix of the constituent cell membranes of living tissues are highly complex and number many hundreds of distinct lipid species. These differ in the nature of the polar group representing the different classes of lipid. Each class consists of a range of molecular species depending on the length, position of attachment and number of unsaturated double bonds in the associated fatty acids. The origin of this complexity is described and the biochemical processes responsible for homeostasis of the lipid composition of each morphologically-distinct membrane is considered. The practical steps that have been developed for the isolation of membranes and the lipids there from, their storage, separation, detection and identification by liquid chromatography coupled to mass spectrometry are described. Application of lipidomic analyses and examples where clinical screening for lipidoses in collaboration with mass spectrometry facilities are considered from the user point of view.

Keywords: Membrane preparation; Phospholipid; HPLC separation; Tandem mass spectrometry

Contents

Abbreviations: PC, 1,2-diacyl-sn-3-glycerophosphocholine; PE, 1,2-diacyl-*sn*-3-glycerophosphoethanolamine; PS, 1,2-diacyl-*sn*-3-glycerophosphoserine; PI, 1,2-diacyl-*sn*-3-glycerophosphoinositol; PA, 1,2-diacyl-*sn*-3-glycerophosphatidic acid; PG, 1,2-diacyl-*sn*-3-glycerophosphoglycerol; IP3, inositol-3,4,5-trisphosphate; MS, mass spectrometry; LCMS2, liquid chromatography coupled to tandem mass spectrometry; SPE, solid phase extraction; BHT, 2,6-di-*tert*-butyl-*p*-cresol; ESI, electro-spray-ionisation source; APCI, atmospheric pressure chemical ionisation source; MRM, multiple reaction monitoring; CTEP, cholesterol triglyceride exchange protein; LCAT, lecithin cholesterol acyl transferase; EFA, essential fatty acid; CID, collision induced dissociation (fragmentation).

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1. Introduction

Lipodomics is the methodology, analogous to proteomics in the characterization of cellular proteins, able to produce an extensive listing of lipid classes and their distinctive molecular species that are present in a biological sample. The constituents of complex lipids are extremely diverse and the combinations and permutations in which they are assembled in the constitution of individual molecular species of lipid further amplify this diversity.

A priori the characterization of complex lipids, which represent one of the primary structural components of cell membranes, presents a considerable challenge. The underlying strategy involves firstly, the isolation of morphologically-distinct membranes or subfractions there from and, secondly, the extraction of these lipids free from the membrane proteins and other components. The identity of lipids responsible for anchoring and lipids non-covalently attached to a specific group of proteins in membranes is another aspect of lipidomics. Once extracted, the lipids must then be fractionated, usually requiring a multi-step chromatography process, to allow identification and quantitation of the individual molecular species. The intricacy of these operations may be appreciated by the fact that there are 17 or so long-chain fatty acids found associated in complex lipids in human cells which are distributed in pairs in five major classes of glycerophospholipids and there are also six or so very long-chain fatty acids in the various sphingolipids.

The complexity of the task is exemplified by the human red cell which contains only a plasma membrane [1]. This membrane is known to contain in the order of 300 molecular species of glycerophospholipids formed by different long-chain (C14–C22) fatty acids each present at a level exceeding 2% of the total fatty acids. The fatty acids are linked by ester bonds with the major phosphatidyl moieties found in PC, PE, PS, PI, PA classes. The role of each molecular species resulting from a particular combination of a polar headgroup and two acyl chains, located at specific carbon atoms of the glycerol, of particular length and number and position of unsaturated bonds, on the properties of the membrane is poorly understood. In addition to glycerophospholipids, a variety of sphingolipid classes is also found amidified by many minor fatty acid species such as branched- or hydroxylated-fatty acids (<1 mol%). The profiling of fatty acids in red cell membranes has been recognized for some time as a diagnostic indicator of essential fatty acid deficiency in children and has become a routine test long before the role of the molecular diversity of membrane lipids had been fully appreciated. The same tentative approach is inferred for the developing lipidomics field at a time when not all bioactive lipids have yet been discovered. Lipids considered initially as the building material of membranes or as a fuel for bioenergetics are now frequently regarded as a potential reservoir for precursors of signaling second messengers. This could represent a clue for understanding the molecular diversity observed in membrane phospholipids. Subtle biophysical properties are also another possible explanation especially with reference to the emerging field of heterogeneous membrane domains.

Other applications of lipidomic technology include tracing of lipid metabolites such as detection of a particular lipid present in low proportions and subject to rapid turnover, for example, inositol-1,4,5-trisphosphate (IP3). Another example is the production of eicosanoids from arachidonic acid derived from precursor arachidonic acid. Lipidomics can also be applied to trace the interconversions that operate between lipid classes such as the transformation of PE to PC by successive methylation of the amino group of PE or the attachment of sugar residues in glycosphingolipids. These applications can be categorized into a separate group referred to as ''Metabolomics'' which utilizes the general methodology applied to establish metabolic pathways. A notable difference from conventional methods, however, is that recent methods of lipidomics do not necessarily employ tracers or probes like