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Lipidomics: when apocrypha becomes canonical

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Lipidomics is a branch of the field of metabolomics. Although only about a decade since its inception, lipidomics has already had a major influence on the way in which questions about lipid metabolism and signaling are posed. The field is intertwined in the culture and rich history of mass spectrometry. Early work emphasized analytical issues such as limits of detection and numbers of molecular species quantitated in single injections. Increased sophistication in applications of lipidomic analysis and emerging technologies, such as imaging mass spectrometry, are facilitating the study of lipid metabolism and signaling species in cellular functions and human diseases. In the coming years we anticipate a richer understanding of how specific lipid species mediate complex biological processes and interconnections between cellular pathways that were thought to be disparate.

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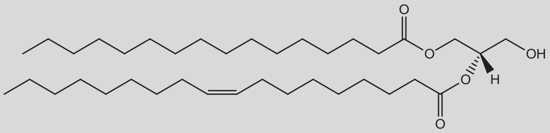
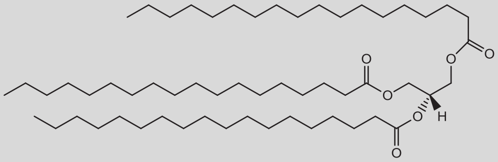
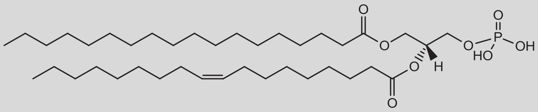
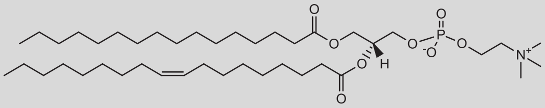
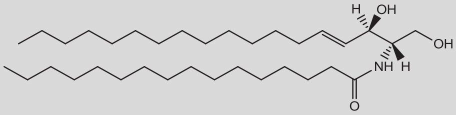
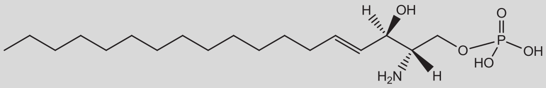
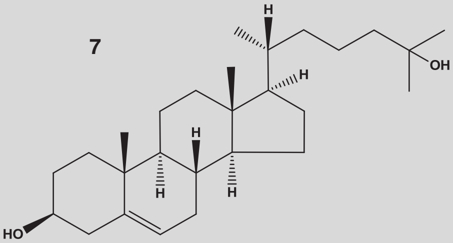
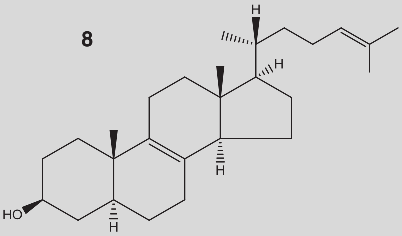
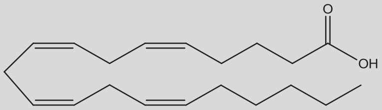
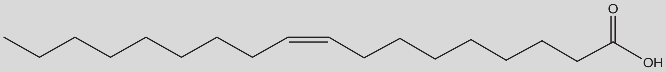
Background and history

Lipidomics is the systematic identification of the lipid molecular species of a cell, organelle, globule, or whole organism with emphasis on the quantitative determination of composition changes in response to a perturbation, such as stimulation of a receptor-mediated signaling pathway or alteration in metabolism. Since the first use of the term over a decade ago there has been controversy as to what truly constitutes 'lipidomic' analysis, but most of the early contributors agree that the origins emerged from instrumentation advances in mass spectrometry, and computational biology. The ability to identify lipid molecular species and track changes in the composition of a cell membrane or biopsied tissue are rooted in the technological revolution of mass spectrometry instrumentation, particularly electrospray ionization mass spectrometry. Development of next generation instruments that could be used beyond the confines of advanced analytical chemistry laboratories, allowed the technology to be increasingly used by researchers in the biological sciences. Several investigators made major contributions to the methodology that has led to mass spectrometry as the preferred method of lipid identification (see reviews [1,2]) but in the late 1990s a transition began that engaged the power of systems biology in the quantitative analysis of lipids. As advances in the sensitivity and resolving power of mass spectrometry progressed, investigators pursued systematic identification of the lipomes of various cell types. An influential paper by McLafferty and colleagues [3] demonstrated the use of positive and negative mode Fourier-transform ion cyclotron resonance mass spectrometry (FTICR-MS) to identify the glycerophospholipid composition of a mucosal mast cell line. Subsequently, Ivanova *et al.* [4••] expanded this capability by tracking a greater number of species and measuring changes in multiple species during the process of regulated exocytosis. In 2001 the National Institute of General Medicine (NIGMS) formally sponsored the creation of a Lipidomics Core as part of the large-scale collaborative initiative program, The Alliance for Cellular Signaling. This program was designed to define the components of signaling systems and describe the complex overlapping physical and regulatory interactions between these components in a quantitative manner [5] and quantitation of lipid species was acknowledged as critical element necessary for a comprehensive systems analysis of cellular signaling networks.

The early goals in lipidomics were oriented on technology development and building the infrastructure for the analytical and computational challenges [6,7]. The field has rapidly progressed and increasingly is being used to address questions in diverse biological systems. From its somewhat esoteric origins lipidomics has gained acceptance as previously unappreciated roles of lipid species in cellular processes are being discovered and molecular mechanism described. Among the contributions of the NIGMS-supported Lipid Metabolites and Pathways Strategy (LIPID MAPS) project has been the reorganization of lipid classification to facilitate bioinformatic organization and making databases more compatible with search functions [8]. A review on the structural organization of the Lipidomics database and online tools provided in the LIPID MAPS database (http://www.lipidmaps.org/) was recently contributed by Subramaniam *et al.* [9]. This includes an in-depth discussion of the various issues related to classification, ontology, nomenclature, and structural representation of lipid molecules that were considered in the creation of the database.

Table 1

Major lipid classes. Major lipid classes (with representative species shown) as organized by the LIPID Metabolites And Pathways Strategy (LIPID MAPS) consortium. This consortium has defined the mouse macrophage lipidome (an inventory of thousands of lipid molecular species) and worked to develop state-of-the-art lipid analysis protocols, developed website-based tools (www.lipidmaps.org), and increased access of the broader scientific community to lipidomics (see further details in Ivanova *et al.* [17]; Myers *et al.* [18]).

Lipid classification	Representative species
Glycerolipids	**1**  **2**  **[1] Diacylglycerol (DAG) and [2] Triacylglycerol (TAG)**
Glycerophospholipids	**3**  **4**  **[3] Phosphatidic Acid (PA) and [4] Phosphatidylcholine (PC)**
Sphingolipids	**5**  **6**  **[5] Ceramide (Cer) and [6] Sphingosine-1-Phosphate (S1P)**
Sterols	**7**  **8**  **[7] 25-Hydroxycholesterol and [8] Zymosterol**
Fatty acids/eicosanoids	**9**  **10**  **[9] Arachidonic Acid (20:4) and [10] Oleic Acid (18:1)**