Abstract

It is clear that some of the greatest intellectual challenges of the 21st century will center around biological sciences and medicine. Lipidomics is a new ‘omics.’ Although this name was coined only recently, the importance of the systems biology of lipids is now widely recognized.

Introduction

Lipidomics is an exciting emerging area with vast potential. Lipid research has been boosted by an impressive string of recent achievements and developments. Elegant studies in model organisms have provided us with mechanistic insight into lipid action at the molecular level. Technological advancements, particularly in the field of analytical methodology, are opening new ways for lipid detection at unprecedented levels of sensitivity and specificity. Furthermore, it is becoming increasingly clear that deregulated lipid metabolism plays an important role in many human ailments such as heart disease, cancer and diabetes, and neurological disorders. The convergence of these developments in lipid research offers rich opportunities for research and lipid-targeted drug development.

Lipidomics — New Frontiers in Lipid Research

Biology of Lipids

Heart disease, for example, has been intimately linked to cholesterol metabolism via its connection to low-density lipoprotein (LDL) trafficking and uptake. The regulation of de novo cholesterol biosynthesis is now relatively well
understood at a mechanistic level. Statins such as inhibitors of key enzymes in cholesterol synthesis lead to reduced levels of LDL and lowered risk of heart attacks. Over the past 30 years, basic research in cell biology has been a major driver of lipid research not only with respect to cholesterol. Elegant experiments in model organisms including yeasts, worms, flies, and mice have provided deep insight into lipid metabolism in living organisms. Using modern genetic approaches in combination with cell biological and functional assays, these studies have addressed the roles of many lipid enzymes, including lipases, kinases, phosphatases, transferases, etc. in membrane trafficking and cell signaling. Common to these studies is their focus on mechanistic aspects, which is key to the understanding of the biology of lipids at a molecular level.

**Technological Advances**

In more recent years, these developments have been supported by technological advances. In particular, novel biochemical methods based on chromatography and mass spectrometry are beginning to revolutionize the field of lipid research. Never in the past has it been possible to detect, characterize, and quantify lipids at such high levels of sensitivity and resolution. It is starting to become clear from these new approaches that the ‘world of lipids’ is very large and diverse. Nature is synthesizing an enormous number of chemically and structurally distinct ‘lipid species’ (Fig. 1). One important characteristic that contributes to this diversity lies in the multiple combinations of different functional headgroups (e.g. inositol, serine, choline, etc.) with fatty acyl chains of varying length and degree of chemical saturation (e.g. palmitic acid, oleic acid, arachidonic acid, etc.). It is here where the novel analytical methods make a great contribution. Mass spectrometry in particular now allows measurement of hundreds of lipids selectively and quantitatively in a single experiment. The lipids are discriminated based on their masses which can be measured very accurately.

In addition to new technological platforms for lipid analysis, there are increasing numbers of novel reagents. Pure and synthetic lipid standards serve as standards, and are critical for the quantification of natural compounds. Many phospholipids, ceramides, and increasingly also glycolipids, are now commercially available in microgram and milligram quantities. Functionally modified lipids such as activatable lipids, fluorescent derivatives, and radio labeled compounds serve in a wide variety of applications in basic research and the drug development process, such as in high-throughput assays of enzyme activities.
Applications of Lipidomics

Of great future interest will be the development of a better understanding in how well alterations in levels of lipids are tolerated within physiological boundaries. It is clear that lipid synthesis and metabolism are tightly regulated in living organisms, but for many lipids it is not clear precisely to what degree. In addition, since many lipid metabolic pathways are interconnected, it is conceivable that perturbation at ‘one end’ will also lead to changes at other positions in the lipid maps. In fact this precisely is one of the central aims of many, if not most, current investigations of biochemical lipidomics.

There is increasing awareness of the wide applicability of lipidomics. Profiling of lipids on a systems-level scale (lipidomics) can help to identify metabolic pathways which are activated or deactivated when a cell (or tissue) is shifted from its physiological condition to another physiological (or pathological) condition (pathway/target discovery). A better understanding of the regulation of underlying (lipid) metabolic pathways can help to design strategies for intervention. The levels of lipids which are making up biomembranes in our cells and tissue and others which are circulating as signaling molecules in our blood are reflective of the physiological state during a given point in time. Thus, careful analysis of lipids (and lipid metabolites as well as their oxidized derivatives) is likely to yield novel biomarkers. Since lipid metabolism is involved in almost all major diseases, such lipid-based biomarkers will provide important novel information, which thus far is limited to the other components of the living system, namely the proteins, nucleic acids, and sugars.

We will also see novel classes of inhibitors (small molecules as well as antibodies) which interfere with lipid enzymes and cascades of lipid signaling. PI 3-kinases and sphingosine kinase inhibitors, for example, are in development by major pharmaceuticals as well as biotechnology companies focusing on lipid signaling. It is likely that the above two pathways will be complemented by others, such as lipid phosphatases, lipases, and transferases.
Lipidomics — An Interconnecting Field in the Life Sciences

All these developments are reflected by an increasing awareness of the importance of this new field. Many major conferences in basic biology and life sciences now have sessions devoted to lipid research and lipidomics. In addition, there are numerous recent workshop-style symposia which are being held in many countries around the world. These symposia are founding events, and typically attract academic and corporate investigators as well as engineers involved in software and hardware development of research instruments.

The 1st Singapore Lipid Symposium (1st SLS) was held in February 2006 at the National University of Singapore (NUS) in conjunction with national research institutes from A*Star and Temasek Life Science Laboratories. This three-day symposium brought together cell biologists, biochemists, and biophysicists from leading laboratories worldwide to share and discuss the latest research advances in the field of lipidomics. By bringing investigators from a spectrum of disciplines and backgrounds, this workshop-style forum was an excellent platform for the open exchange of ideas that will spur lipidomics to the next level.

Indeed, due to the breadth of expertise required, many of the pace-setting initiatives in lipidomics are collaborative endeavors that are multi-investigator, multi-institutional, or multi-center in nature. From North America, the principle investigators of LIPIDMAPS (www.LIPIDMAPS.org), a consortium with a mission to comprehensively measure all of the lipids in a human cell line, presented at the 1st SLS. From Europe, we had members of the European Lipidomics Initiative (ELIfe, www.lipidomics.net). ELIfe aims to bring together technological know-how in academia and industry, mainly through organizing symposia and workshops such as the SLS. Delegates from Japan presented their initiatives which deal with the development of databanks and search engines that are needed to analyze and archive the vast amount of biochemical data on lipid measurements and profiles (e.g. www.lipidbank.jp). And of course, these major initiatives build on (and complement) cutting-edge research by individual laboratories around the world. Many of these investigators were present at the 1st SLS as well (www.lipidprofiles.com).

As one of the fastest-growing areas of research in both industry and academia, the biomedical sciences are rapidly spawning collaborations that transcend disciplines, geography, and cultures. Already a node for international flows of trade, finance, and transportation, Singapore — leveraging on its strategic location at the crossroads of Asia — is taking steps to build a vibrant, world-
A new R&D strategy and agenda for Singapore has been recently unveiled with the launch of the National Research Foundation (NRF). Public sector funding for research, development and innovation will more than double to S$13.5 billion over the next five years.

Indeed, Singapore could very well play an important catalyst role in lipidomics by advancing interactions with other initiatives and with the growing community in the Asia Pacific. In addition, many biomarker studies will likely include cohorts of multiple ethnic backgrounds, and Singapore will thus be well placed to play a key role in such studies. As a country in the heart of Southeast Asia, it continues to be immersed in an environment which harbors many infectious diseases. I hope that lipidomics will also contribute to R&D efforts in this area as many pathogens, in particular those which reside and replicate within cells, depend on transport across lipid membranes and intracellular trafficking.

Natural lipids exist in many different chemical and structural forms. Shown here are representative examples grouped according to a recently proposed nomenclature. a. Fatty acyls (FA) are integral components of many lipids. They themselves form an important class of signaling molecules, which mediate many inflammatory processes (‘lipid mediators’). In fact, a subsection of lipidomics which focuses on fatty acyls and their derivatives is sometimes referred to as ‘mediator lipidomics’. Shown here is the structure of the prostaglandin endoperoxide PGH2. b. Glycerolipids (GL) are subclassified by the number of fatty acyl chains: monoradylglycerols (MG), diradylglycerols (DG), and triradylglycerols (TG) are important in the storage of chemical energy. MG and DG also play roles in
intracellular signaling. The structure of a common molecular species of TG in animal fat, TG with palmitic and oleic acyl chains, is shown (TG 16:0/16:0/18:1). c. Glycerophospholipids (GP) carries functional headgroups that are linked to the glycerol backbone via a phosphate group, and this class includes phospholipids which are important components of cellular membranes (e.g. phosphatidylcholines, phosphatidyserines, etc.). A common phosphatidylinositol (GPIns) with palmitic acid and oleic acid is shown (GPIns 16:0/18:1). d. Cholesterol is a major sterol in mammals, and is commonly found in its ‘free’ form (shown) or esterified to fatty acyls (sterol esters), of which cholesteryl linoleate is one of the most abundant species in human plasma. Other prominent members of sterol lipids (ST) include secosteroids (Vitamins D2 and D3 and derivatives) and bile salts. e. Sphingolipids share a sphingoid base backbone as a common feature. Shown is the structure of a complex glycosphingolipid found in the yeast S. Cerevisiae. This molecule contains inositol and mannose phosphates on top of its ceramide backbone. f. Prenol lipids are synthesized from 5 carbon precursors, and are common lipids found in bacteria and plants. The structure of Vitamin K2 (menaquinone 6) is shown. Vitamin K2 contains an isoprenoid tail and a quinonoid head, and acts as an electronic carrier in bacterial membranes. g. The term “saccharolipids” was proposed recently to catalog compounds in which fatty acyls are directly connected to sugars. Into this classification falls Lipid A (shown), an anchor part of lipopolysaccharides in Gram-negative bacteria.

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