Lipidomics: A New Window to Biomedical Frontiers

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ABSTRACT

Lipids are a highly diverse class of molecules with crucial roles in cellular energy storage, structure and signaling. Lipid homeostasis is fundamental to maintain health, and lipid defects are central to the pathogenesis of important and devastating diseases. Newly emerging advances have facilitated the development of so-called lipidomics technologies and offer an opportunity to elucidate the mechanisms leading to disease. Furthermore, these advances also provide the tools to unravel the complexity of the 'allostatic forces' that allow maintenance of normal cellular/tissue phenotypes through the application of bioenergetically inefficient adaptive mechanisms. An alternative strategy is to focus on tissues with limited allostatic capacity, such as the eye, that could be used as readouts of metabolic stress over time. Identification of these allostatic mechanisms and pathological 'scares' might provide a window to unknown pathogenic mechanisms, as well as facilitate identification of early biomarkers of disease.

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Introduction

Lipids are a diverse group of compounds with many key roles enabling them to serve as forms of energy storage, structural moieties and signaling molecules [1] (Figure 1). Lipids are broadly defined as hydrophobic or amphiphilic small molecules that originate either entirely or in part from two distinct types of building blocks: ketoacyl and isoprene groups [2]. Lipids are structurally highly diverse owing to the many possible variations of the lipid building blocks and how these blocks are linked. We have conservatively estimated that the theoretical number of lipids covering major lipid classes is close to 200 000 [3]. Lipids are very abundant in biological systems, constitute ~50% of the mass of most animal cell membranes[4] and exhibit an important degree of specialization in specific cellular compartments [5]. Maintenance of an appropriate lipid composition in the cellular membranes is required to ensure membrane fluidity, topology of attached proteins, activity of membrane-bound enzymes, degree of exposure of surface proteins, lateral mobility of receptors and activation of specific signaling pathways. Interestingly, despite being exposed to the diverse nutritional composition of organismal diets membranes maintain a remarkable control of their lipid composition, which reinforces the concept that specific mechanisms exist to ensure the maintenance of the homeostasis of the lipid composition of membranes.

The development of a pathological state represents a situation of biological stress associated with the breakdown and failure of the mechanisms controlling homeostasis. Given the tight homeostatic control of lipid metabolism and its enormous structural and bioenergetic relevance it is not surprising that alterations in lipid metabolism play important roles in the pathogenesis of most of the common diseases, including insulin-resistant diabetes [6,7], Alzheimer's disease [8,9], schizophrenia [10,11], cancer[12,13], atherosclerosis [14] and toxic manifestations of infectious diseases[15,16]. It is interesting to note that some of these apparently diverse diseases tend to cluster together in the same individuals, a phenomenon known as the metabolic syndrome (MetS) [17].

The prevalence of the MetS, defined as the coincidence in the same individual of obesity, insulin resistance, dyslipidemia, hypertension and increased cardiovascular morbidity, is increasing exponentially within several populations worldwide, with a profile that could be considered of epidemic proportions[18]. This profile clearly indicates that in addition to undeniable genetic contribution, other environmental factors, such as nutrients and inactivity, are likely contributors to the progressive acceleration of MetS. Despite its obvious public health and economic implications and worldwide research efforts, the sad truth is that the molecular mechanisms linking all these manifestations are still

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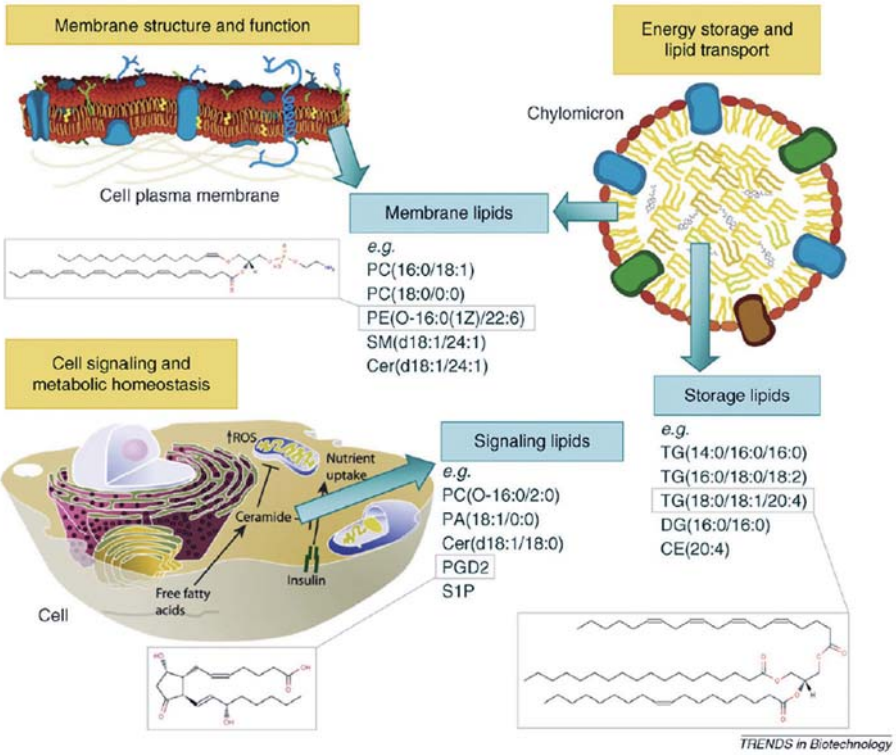

Fig.1 Diverse biological roles of lipids, with a few common representative molecular species listed. The chemical structures are shown for ethanolamine plasmalogen PE (O-16:0 (1Z) / 22:6), prostaglandin D2 (PGD2) and triacylglycerol TG (18:0 / 18:1 / 20:4). PC, phosphatidylcholine; PE, phosphatidylethanolamine; PA, phosphatidic acid; DG, diacylglycerol; Cer, ceramide; SM, sphingomyelin; ChoE, cholesterol ester; S1P, sphingosine-1-phosphate.

elusive; in part because of the difficulty in discriminating primary pathogenic events from secondary allostatic responses. However, in recent years, accumulating evidence suggests that lipids, and more specifically their toxic effects when they excessively accumulate in areas other than the adipose tissue, might provide vital clues to understand the pathogenesis of the MetS [19]. The key concept of a pathogenic framework is lipotoxicity [20,21]; the toxicity produced by lipids that cause insulin resistance when accumulated in metabolically relevant organs such as skeletal muscle, liver, pancreatic b cell or vascular wall. In those organs, the accumulation of lipids not only distorts specific signaling pathways, such as insulin action and or other growth factors, but also induces important allostatic responses in an attempt to maintain energy homeostasis.

Traditional approaches to the study of lipids have relied on analyses that were specific to a lipid class, or to a particular fatty acid composition, and thus have likely addressed only a small fraction of the lipid complexity important in the physiological context. Here we suggest that the new technology platforms and bioinformatics tools that are becoming available for the study of lipids offer an opportunity to provide a sensitive readout of integrated metabolic stress over time, as well as to unravel the complexity of the allostatic forces that allow maintaining normal phenotypes at the expense of highly expensive adaptive mechanisms (Box 1). Identification of these allostatic mechanisms and pathological insults might provide an invaluable window to novel pathogenic mechanisms as well as helping to identify early diagnostic and prognostic biomarkers of complex diseases.

The emergence of lipidomics

Owing to their central biological role, lipids have been anintense area of research since the 1960s, yet since that era have been somewhat overshadowed by the advent of molecular biology, genomics and proteomics. The major bottleneck in lipid research has been the unavailability of sensitive analytical platforms capable of detecting the intact lipid molecular species in specific biological systems.

Glossary

Allostasis: allostasis is the process of achieving stability, or homeostasis, through physiological or behavioral change (Box 1).
Aqueous humor: a thick watery substance located between the lens and the cornea (Figure 2a).
Avascular: not associated with or supplied by blood vessels.
Biomarker: a substance used as an indicator of a biologic state. It is a characteristic that can be objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Effector: a molecule that activates, controls, or inactivates a biological process or action.
Glycemia: concentration of glucose in the blood.
Homeostasis: the property of a living organism that regulates its internal environment so as to maintain a stable, constant condition.
Hyperglycemia (or high blood sugar): a condition in which an excessive amount of glucose circulates in the blood plasma.
Hypoxia: a shortage of oxygen.
Lipotoxicity: accumulation of (lipo) toxic reactive lipids such as ceramides in nonadipose tissues of metabolically important organs, such as pancreas, skeletal muscle, liver, and heart.
Nuclear cataract: a clouding that develops in the nucleus, the center of the eye lens. It can vary in degree from slight to complete opacity and obstruct the passage of light.
Prodromal period: the time during which a disease process has already begun, but is not yet clinically manifest.

Additionally, owing to their tight homeostatic control, even relatively small changes in the concentration of lipids –of the order of ±10 % – can be physiologically significant. Thus, the study of lipids in a biomedical context requires the availability of platforms that can accurately and comprehensively quantify the lipids. The advent of modern analytical techniques for metabolomics[22,23], empowering us with the ability to detect and quantify hundreds of intact lipid molecular species in parallel, has thus rejuvenated the field of lipid research over the past decade and has led to emergence of lipidomics [24–26] (Box 2).

Owing to these technological advances, lipidomics is currently at the stage where vast amounts of data are

Box 1 Allostasis

The concept of allostasis refers to maintenance of stability through change. This concept could be applied to multiple fields spanning from sociological networks, animal behavior, or more relevant for this Opinion, to metabolic diseases. The concept of allostasis was introduced by Sterling and Eyre to describe the adaptive mechanisms that allow maintenance of normality at the expense of robust, energy-costing adaptive mechanisms [33]. Whereas the concept of homeostasis refers to mechanisms that prevent change and ensure the maintenance of the ideal steady state of a function (e.g. pH, dissolved oxygen), allostasis refers to the changes that are required in response to severe challenges and are aimed at restoring the homeostasis of the system. Working under allostatic conditions is expensive, and the cost has been defined as the allostatic load of a system. The allostatic load refers to the cumulative stress derived from the activation of adaptive changes to maintain the functionality of the system. Allostatic load is proportional to the inefficiency of the allostatic mechanisms and to the intensity of the challenge. Depending on the strength or conversely the fragility of a biological system, the allostatic load can be either tolerated or not. In particularly vulnerable biological systems, the allostatic load results in allostatic overload which is proportional to the risk of global failure of the system, or in biomedical terms, to the development of disease. Contributing factors to the allostatic load are the organ specific genetic make up, the environmental experiences during early development, cultural impact on life style choices with regard to diet, exercise, smoking and drinking. All of these factors influence the charge of the allostatic reactivity of the biological system. Thus allostatic load reflects a genetically or developmentally programmed inefficiency to respond to environmental challenges.

becoming available, yet the tools and the knowledge needed to interpret these data in their biological context are lacking to a large extent. The particular difficulty of a bioinformatic analysis of data obtained from lipidomics stems from the fact that the measured lipid concentrations reflect regulation at multiple spatial and dynamic scales, for example global changes in cell membrane composition, systemic lipid metabolism, lipid trafficking, lipid oxidation or biochemical reactions. Even at the biochemical level, available metabolic pathway databases such as KEGG (Kyoto Encyclopedia of Genes and Genomes) [27] do not capture lipids and their reactions with the degree of structural detail that can be detected with the current lipidomics technologies[28,29]. New tools are therefore needed to decipher the obtainable information on lipids at the molecular level. The LIPID MAPS consortium (LIPID Metabolites And Pathways Strategy; http://www.lipidmaps.org/) recently proposed a new naming system for lipids [2] that assigns a unique 12-character signature for biologically relevant lipids. This unique identification number for a lipid provides valuable information, such as source of database, lipid category, class, subclass and numbers specific to the particular lipid. The LIPID MAPS system therefore enables to efficiently store and process information on a vast amount of different lipids. This new nomenclature system is expected to further the field because it enables automated processing of lipid information, which is needed for dealing with vast amounts of data being generated by lipidomics platforms.

To address the problem of lipid pathway mapping at the molecular level, we recently developed a lipid pathway instantiation strategy [28]. Using this approach, the global lipidomics data are first analyzed using multivariate statistical methods. Clusters of lipids that are co-regulated under specific physiological conditions are so identified, and biochemical pathways can then be reconstructed for specific lipids from the clusters of interest. Future strategies for modeling of lipidomics data will probably require the combination of multiple biocomputational strategies, such as pathway reconstruction [28], modeling of systemic lipid metabolism [30,31] and biophysical modeling [32].

Box 2. Lipidomics technologies in brief

The analytical strategies for the study of a lipidome can be divided into two overlapping categories: global and targeted lipidomics.

(1) Global lipidomics aims at rapid identification and relative quantification of hundreds of molecular lipids across multiple structural classes, usually sourced from the total lipid extracts. The global strategies include 'shotgun lipidomics,' which uses direct infusion of lipid extracts into a mass spectrometer [48,49], as well as liquid chromatography coupled to mass spectrometry (LC–MS) [50,51].

(2) Targeted lipidomics aims at quantitative analysis of either a single or several selected lipids, e.g. within a specific lipid class [52,53].

Data processing, which consists of peak detection, spectral alignment, normalization, and identification, is an essential part of global and quantitative lipidomics platforms. Software packages used for metabolomics data processing, such as MZmine [54] or XCMS [55], have been commonly applied to LC–MS-based approaches. Specialized lipidomics software solutions have also been developed for specific analytical strategies [56,57]. Among the many exciting technological developments in lipidomics, the ozone-induced dissociation (OzID) [58] technique promises to solve the problem of an exact structural determination of numerous lipids by determination of the position of the double bonds. Double bond positioning is particularly important in structural elucidation of plasmalogens, i.e. the endogenous antioxidants [59], or for distinguishing closely related fatty acids within lipid molecules of the same mass and functional class, e.g. the v-3 and v-6 fatty acids.

Lipids: a physiological view

The maintenance of the membrane lipid composition despite nutritional and other environmental stresses constitutes a good example of an allostatic change, which as first introduced by Sterling and Eyer [33] is defined as an adaptive process aimed at effectively maintaining stability through changes in specific regulatory mechanisms. Typically, such allostatic adaptations are designed to induce short-term corrective changes to regulatory systems. However, when activated for long periods, for example during chronic states of overnutrition or undernutrition, the maintenance of lipid homeostasis might actually be achieved at the expense of a metabolic cost, or 'collateral damage,' defined by McEwen as allostatic load [34–36]. For instance, maintenance of allostatic changes might induce permanent changes in the default setting of the biological system that could prevent an appropriate shut down after the stimulus has been discontinued. Another undesired effect of allostatic load might the inappropriate activation of alternative biosynthetic pathways, which could lead to the accumulation of

unnecessary lipids.

There is evidence that the maintenance of lipid membrane composition is tightly regulated by complex mechanisms involving several transcription factors (TFs), such as sterol regulatory element binding proteins (SREBPs), whose activity is further modulated by sensitive sensory systems in response to changes in lipid levels[37,38]. Interestingly, it has been observed that genetic ablation of the gene encoding SREBP1, the TF that regulates preferentially fatty acid metabolism, is compensated by upregulation of SREBP2, the TF preferentially controlling cholesterol metabolism, with the consequence that inappropriate amounts of cholesterol are accumulated. This on the one hand can be interpreted as an example of the tightness of the control in lipid metabolism, but on the other hand can serve as an example of collateral damage caused or allostatic load produced through an inappropriate activation of the cholesterol pathway in an attempt to maintain the homeostasis of fatty acids.

Thus, the allostatic load derived from the allostatic adaptations, together with a specific genetic make-up and in the context of specific developmental stages (e.g. early-life experience, puberty, pregnancy, menopause, aging), metabolic status (e.g. obesity) or bioenergetic demands of an individual, might define different degrees of vulnerability to disease. In the course of our research, we have observed that, although these lipid-related allostatic mechanisms can use similar effectors, they might involve different pathways in different organs that are defined by their specific genetic repertoire. This confers an additional layer of complexity to the analysis of lipids, but by contrast opens new opportunities for selective interventions to ease the allostatic load [7, 28, 39].

Despite the obvious biological importance of allostatic loads, there is a paucity of data for the underlying allostatic mechanisms that ensure the maintenance of the cell membrane lipid homeostasis, and how these mechanisms are adapted to specific nutritional and metabolic perturbations. The recent advances in lipidomics technology offer a unique opportunity not only for the biochemical characterization of lipids but also for a more comprehensive understanding of the influence lipids have on a biological system, such as their effects on cellular membranes with respect to membrane architecture, transcriptional and translational modulation, cell signaling, cell–cell interaction and response to environmental change over time. Given the nonlinearity of the allostatic mechanisms, the main challenge is to determine how the different effectors of the allostatic response are modulated dynamically with the level of change of each of the effectors. In this regard, lipidomic analysis in the context of a systems-biology approach offers an unprecedented opportunity to elucidate the complexity of the allostatic mechanisms involved in maintaining lipid homeostasis.

Eye lipidome: a window to the past

The lipidome of an organism varies with gender, age and lifestyle. In early childhood, multiple changes in the constitution of circulating lipids reflect rapid developmental and environmental changes [40]. In older individuals, the lipidome is characterized by a decrease in the proportion of antioxidant lipids, thus reflecting the increase of oxidative stress with age [41]. One of the main challenges the healthcare industry faces is to be able to develop and apply effective preventive medicine. For this, early diagnostic and prognostic biomarkers are required to identify those individuals who will benefit the most from early intervention. Most common diseases are preceded by a long prodromal phase during which no objective symptoms are evident. For example, development of diabetes towards common forms of type 2 diabetes is preceded by a variable period during which insulin resistance is appropriately compensated by the secretion of the hormone insulin to maintain normal glycemia [42]. It is currently unclear which individuals amongst patients will evolve towards overt diabetes, or who will exhibit a severe cardiovascular outcome. The occurrence of visible symptoms, such as hyperglycemia or the development of atherosclerotic lesions, are late events in the progress towards the symptomatic disease. By contrast, we believe that there is an invaluable opportunity to use some of the early allostatic responses as markers of an allostatic load, which could be correlated to a quantified risk of disease progression.

An alternative to the use of allostatic responses as biomarkers could be a focus on tissues and organs with decreased allostatic capacity that, in this respect, are more suitable to record the 'scares' of the pathological insult. On one hand, from a Darwinian point of view, it is obvious that important metabolic organs, which are under pressure to perform regular and essential metabolic functions, are likely to have been selected to adapt more rapidly and fully, thus making it more difficult to detect early pathogenic mechanisms or past insults. On the other hand, metabolically less active organs, but with a specialized function, such as the lens, which is avascular and needs to maintain transparency, tend to be deprived of the common allostatic adaptive mechanisms[43] (Figure 2a). In this regard, the lens can become a reporter of integrated metabolic stress over time.

In the lens, the progressive accumulation of sphingolipids might cause the lipid hydrocarbon chain regions to become more ordered with age and cataract, which lowers its vulnerability to oxidative damage. Probably partly due to its diminished allostatic control, the lens lipid composition is tightly controlled evolutionarily. In fact, the lifespan of many species has been found to positively correlate with the sphingolipid content in the lens (Figure 2b), and inversely correlate with the lens phosphatidylcholine, which is known to be more prone to oxidative damage [44].

The lens obtains most nutrients by diffusion from aqueous humor and metabolites must often diffuse over long distances to reach the lens cells. Another relevant aspect of lens metabolisms is

the hypoxic environment around the lens, which appears to regulate the rate of lens growth and might also be important for protection against nuclear cataracts. Interestingly, lipoproteins are present in aqueous humor [45] and might undergo oxidation in certain systemic diseases, including renal failure, type 2 diabetes, atherosclerosis, inflammation and aging. We therefore predict that thorough studies of lens lipids and their surrounding fluids with modern lipidomics techniques [46] could be a novel approach able to identify novel early pathogenic insights or biomarkers related to multiple complex diseases that are characterized by long prodromal periods.

The currently used mass spectrometry techniques for lipidomic analysis demand complex sample preparation before analysis and are thus not suitable for the noninvasive determination of lens lipid composition in vivo. A promising technique, Fourier transform near infrared spectroscopy (FT-NIR), has recently been adapted to enable noninvasive measurement of body fat [47]. Although less sensitive and selective than mass spectrometry based methods, the use of optical techniques such as FT-NIR could constitute a feasible strategy for biomarker screening of lens lipids in a clinical setting. Complementarily, mass spectrometry based methods could be applied to study eye lipidomes in nonclinical studies, as well as to accurately quantify lipids in eye fluids, such as in aqueous humor.

Concluding remarks

There is evidence that lipid homeostasis is fundamental to maintain health and that defects in lipid metabolism and homeostasis are involved in the pathogenesis of important and devastating diseases. However, there has been a paucity of knowledge with regard to the role of lipids compared with that of other more easily addressable fields, such as genetics or protein chemistry. This lack of information is not the result of its irrelevance, but in fact the result of the intrinsic difficulty to quantitatively analyze lipids. For many years, the bottleneck of lipid research was the lack of highly sensitive analytical platforms able to provide accurate identification and quantification of lipids with roles in health and disease. The recent development of lipidomic platforms together with biocomputational tools to model metabolism and disease pathways offer an unprecedented opportunity to overcome this bottleneck. The power of the new profiling technologies linked to improved modeling tools offers an unprecedented opportunity to unravel the complexity of the allostatic forces that allow to maintain normal phenotypes at the expense of costly adaptive mechanisms. We have argued here that these adaptive mechanisms, besides their role in constituting potential therapeutic targets, might also become suitable early markers of a pathogenic insult. Alternatively, we suggest that a focus on tissues and organs with decreased allostatic capacity, such as the lens, might provide a sensitive readout of integrated metabolic stress suffered over time. Identification of these allostatic mechanisms and pathological insults might provide an invaluable window to novel pathogenic mechanisms as well as serve to provide early diagnostic and prognostic biomarkers of disease.

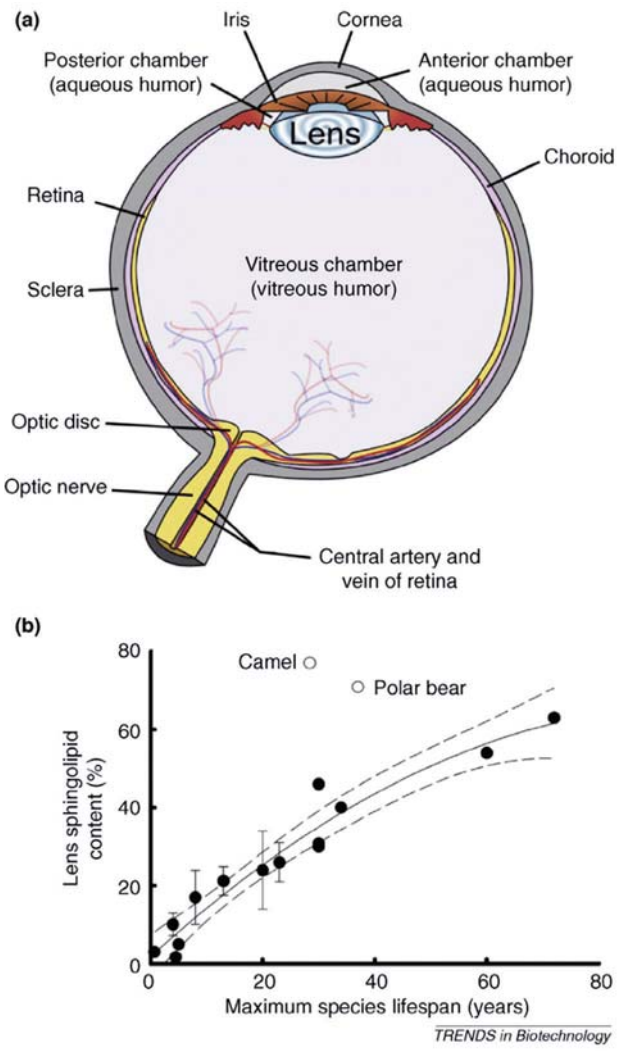

Fig.2 (a) Schematic diagram of the human eye. Only the lens and cornea are avascular tissues under nonpathological conditions. (b) Relationship between differences in lens lipid composition and maximum lifespan of a species, as adopted with permission from Borchman et al. [44]. Each dot in the diagram represents a different species, ranging from roach (0.7 year) and rabbit (4 years) to elephant (60 years) and human (72 years). The horizontal axis represents the maximum lifespan of this species in years and on the vertical axis the percent sphingolipid composition of the lens is shown. The center line indicates the linear regression curve fit with an order of two and the outer lines indicate the 95% confidence limits. Error bars are the standard error of the mean. The figure clearly demonstrates that lens sphingolipid content is related to the maximum lifespan of a species. The lenses of the polar bear and camel have exceptionally high levels of sphingolipids, which is likely due to living in adverse conditions [44].

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