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Title: Time for lipid cell biology

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Abstract: Progress in tools to study lipids in cells is ushering in the prospect of tackling long-standing and important questions in cell biology, from fundamental biology to disease contexts. While we are looking forward to insights into the composition and function of membranes and lipid structures in a plethora of contexts, the need for further methods development comes to light. We asked leaders studying lipid cell biology from different perspectives to share with us what they are most interested in and what the field lacks.

Xiao-Wei Chen - The metabolism and transport homeostasis of cholesterol and phospholipids

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Lipids, although often link to energy stores and obesity, are indispensable building blocks of cellular structures. Phospholipids and cholesterol, in particular, form biological membranes that encapsulate and define cells and organelles. Unlike neutral lipids such as triglycerides, cells cannot store large amounts of amphipathic lipids. Their timely production and distribution, both within and across cells, could therefore be a matter of life-or-death.

Cholesterol offers a prime example of a coordinated homeostasis in metabolism and transport of key membrane-building lipids. Synthesized at the endoplasmic reticulum (ER), cholesterol is efficiently distributed to other membrane organelles, constituting a distinct concentration gradient in which the ER membrane contains the lowest cholesterol content. In specialized cells like hepatocytes and enterocytes, cholesterol traverses the ER membrane to be packed into lipoproteins for secretion. Conversely, when cholesterol is taken up via lipoprotein endocytosis, it is shuttled across lysosome membranes by NPC1/2, and eventually reaches the ER membrane to signal a feedback loop to halt further cholesterol production.

Despite these major advances, fundamental questions remain concerning the spatio-temporal dynamics of cholesterol in cells, partly due to limitations in tools to faithfully track the molecule.

These include how cells transport and distribute cholesterol after its biosynthesis in the ER, or how endocytosed cholesterol reaches and becomes incorporated into the ER membrane to initiate a metabolic signal. Moreover, the questions become more challenging when getting to the nanometer scales, in either vertical or horizontal directions. The precise mechanisms by which cholesterol efficiently traverses bilayer membranes, as well as the function of cholesterol-rich membrane nanodomains awaits further elucidation, especially at the ER where cholesterol content is low. Lastly, one may envision that such coordinated control in the metabolism and transport homeostasis (MATH) may extend to phospholipids and other amphipathic lipids. Understanding such MATH is vital, considering the number of mortalities and morbidities caused by lipid-driven diseases including cardiovascular and metabolic disorders.

Anthony Don - Advances in the application of lipidomics to reveal the etiology of dementia

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This is an exciting time to work in the field of lipid cell biology, as developments in instrumentation and analytical power will soon enable us to study lipid metabolism with single cell resolution. Driven by advances in the speed, accuracy, and sensitivity of mass spectrometry systems, the field of lipidomics has evolved over the past two decades to the point that we can now determine the precise structures for hundreds-to-thousands of lipids in any given sample and employ pulse-chase experiments with stable isotopes to track lipid metabolism in multicellular culture systems or living organisms. In parallel, imaging mass spectrometry now permits the resolution of lipid composition in the low micron range, such that single cell lipidomic analysis in situ is becoming a reality.

One of many biomedical research areas in which this will have tremendous impact is in understanding the etiology of dementia. The brain is one of the most lipid-rich organs and genomic studies tell us in no uncertain terms that gene variants affecting lipid metabolism are the primary determinants of genetic risk for Alzheimer's disease, vascular dementia, and Parkinson's disease. Despite this, there has been very little research on the relationship between these genetic risk factors and brain lipid metabolism for much of the three decades since the discovery that variants in the APOE (apolipoprotein E) gene are the major determinants of genetic risk for Alzheimer's disease. Where lipidomic profiling has been applied to tissue samples, it has thus far failed to convincingly establish how these genetic risk factors combine with ageing to affect brain lipid homeostasis and promote neurodegeneration.

Part of the solution may be to move from cross-sectional lipidomic profiling that measures lipid levels at a snapshot in time to flux experiments that empower us to determine how gene and environment affect lipid synthesis and turnover. Another part of the solution lies in the power of spatial or single-cell technologies to unravel the contribution of specialised cell types to lipid

synthesis, transport, metabolism, and signalling. Combining the two will give us the analytical power to solve complex questions such as the etiology of Alzheimer's disease.

Maria Fedorova – Evolving tools for functional studies of lipids

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With development of high-throughput and sensitive omics technologies, our knowledge on lipid metabolism has increased significantly. Modern mass spectrometry-based lipidomics is capable to annotate several hundreds of lipid species and estimate their concentrations. Despite the wealth of molecular information, functional annotation of lipidomics data remains challenging. Lipids rarely function at the level of single species but rather in a collective manner as supramolecular lipid assemblies, represented by a set of specific molecular species at a given relative abundance. Such lipid assemblies rather than individual lipid species represent the true functional units carrying out a variety of cellular functions. And although, conceptually, it is well appreciated that lipids act collectively (e.g., lipid microdomains in biological membranes), so far there are no practical means to attribute these “lipid collectives” to functional outcomes from lipidomics datasets. Development of bioinformatics tools and application of novel machine learning algorithms will potentially help to define the composition of functional lipid assemblies and facilitate functional annotation of lipidomics datasets.

Another challenge in studying cell biology using lipidomics readouts is that we still have rather limited knowledge on cell type specificity and heterogeneity in terms of lipid metabolism. However, it is crucial for the understanding of metabolic plasticity and discriminating between adaptive and maladaptive responses. Spatial biology including mass spectrometry imaging and single-cell lipidomics will no doubt provide a wealth of information not only on the lipidome composition of different cell types in their native environment, but also will allow to address natural heterogeneity of cellular lipid metabolism. Furthermore, application of lipid flux analysis using stable isotopes and/or biorthogonal labelling technologies (e.g., based on the click chemistry) already delivers valuable information on the close connectivity and temporal regulation of lipid metabolic pathways. Spatial and temporal resolution of lipid metabolism at molecular level will open up new dimensions in lipid cell biology research.

Takeshi Harayama - Structure-function relationship of membrane lipids

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Lipids are extremely diverse in structures, with different backbones, head groups, and tails that vary in lengths, double bond numbers, double bond positions, and hydroxylations. Lipidomics revealed that these lipids are used to generate membranes that differ in composition at multiple scales: organisms, cell types, organelles, membrane leaflets, and distance from membrane proteins. However, besides lipids that are receptor ligands or those that recruit lipid-binding proteins to membranes, the mechanisms by which lipid structures and lipid collective behaviors affect biological processes are rarely elucidated. Therefore, a key question is to establish the structure-function relationship of the numerous lipids present in membranes, which will lead to better interpretations of lipidome changes in various diseases and the corresponding causality.

Mechanisms for how the structures and dynamics of lipid tails affect cellular processes are particularly unclear. For example, in definition, omega-3 and omega-6 polyunsaturated fatty acids differ only in the positions of double bonds, yet their biological roles clearly differ. It is still unclear if their functional differences are mediated by their effects on membrane physical properties or membrane-associated protein functions. Also, there is ample evidence that lipid tails contribute to the generation of lateral heterogeneities (or domains) in membranes, for example in yeast vacuoles, but mechanisms for how heterogeneities emerge are often unclear. It is likely that they result from a complex interplay between lipids, membrane-associated proteins, the cytoskeleton, and other molecules that we still ignore, but we do not know in which order individual factors come into play. Elucidating the roles of lipids in heterogeneity formation will reveal how lipid structures affect membrane trafficking, signaling, organelle functions, and many other processes.

Technically, we need better tools to analyze lipid localization, manipulate cellular lipid compositions, and test how lipids affect the activities of membrane-associated proteins. In particular, tools for unbiased identification of proteins with altered dynamics in distinct cellular lipid environments will be of outstanding interest. Obviously, this asks for a combination of techniques, such as chemical biology, genetic engineering, analytical chemistry, and computational biology. This need for interdisciplinarity is what makes lipid research challenging but also exciting.

Natalie Krahmer – Unlocking the Mysteries of Cellular Fat Storage

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Lipid droplets (LDs), once seen as simple fat stores, are now recognized as key players in metabolic regulation. Over the past decade, research has uncovered the machinery behind LD formation and

degradation, revealed the LD proteome, and how proteins are targeted to LDs. Despite these advances, important questions remain, presenting opportunities for further investigation, especially in relation to diseases.

A challenge is understanding the roles of LD-associated proteins since the function of many of them is still poorly understood. For instance, the physiological functions of PNPLA3 and HSD17B13, well-established risk factors for fatty liver disease, remain unclear. Clarifying their roles could lead to treatment strategies.

Another important aspect is the interaction of LDs with other organelles. These interactions are key for energy homeostasis but remain poorly understood. LDs attached to mitochondria reportedly have distinct proteomes and functions, raising important questions about how these contacts are established and whether and how they control organelle compositions and functions.

LDs show significant heterogeneity across tissues and cell types. For instance, hepatic stellate cells store retinyl esters, while adrenal LDs primarily store cholesteryl esters with unique crystalline structures, raising questions about how lipid composition impacts the LD proteome and function. Even within the same cell type in tissues, lipid storage can vary greatly among cells as it was recently shown for adipose tissue, and LDs within a single cell can differ in size, lipid content, and proteome. Understanding this variability and its physiological significance is crucial.

Beyond lipid storage, LDs play poorly understood roles in signaling and transcription regulation. In adipocytes, LD size affects leptin secretion, critical for maintaining energy balance by signaling the state of fat stores to the brain. However, how LD size is sensed and regulates leptin expression remains a mystery. Addressing these unanswered questions could unlock new insights into metabolic regulation and disease.

Shigekazu Nagata - Exposure of Phosphatidylserine on the Cell Surface

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Biological membranes consist of lipid bilayers that not only separate the extracellular and cytoplasmic spaces but also compartmentalize organelles. The four major phospholipids—phosphatidylserine (PtdSer), phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin—are asymmetrically distributed across the membrane's leaflets. PtdSer is typically confined to the inner leaflet by flippases, enzymes that actively and specifically transport it inward.

During certain biological processes, PtdSer is externalized by scramblases, which randomly redistribute phospholipids across the bilayer. This externalization serves as a crucial signal in various cellular contexts. For example, during apoptosis, cells expose PtdSer on their surface, signaling macrophages to engulf them. While the mechanisms by which apoptotic cells expose PtdSer and how it is recognized by macrophage receptors are well understood, the processes

governing PtdSer exposure in senescent cells remain elusive. In the small intestine, epithelial cells undergoing turnover expose PtdSer to signal their removal, and during neural development, PtdSer exposure precedes the pruning of unnecessary synapses. However, these processes are not yet fully elucidated.

PtdSer also plays a key role in cell fusion events, such as those occurring in osteoclasts, myotubes, and syncytiotrophoblasts, where its transient exposure facilitates membrane fusion. Despite this, the exact molecular mechanisms of PtdSer exposure and its specific role in these fusion events remain unclear.

Activated platelets expose PtdSer and release PtdSer-exposing microparticles, which serve as scaffolds for clotting factors, facilitating their activation. Although the exposure of PtdSer and the production of these particles in platelets are well studied, the mechanisms underlying the generation of other PtdSer-exposing cells and particles—such as activated T cells, milk fat globules in mammary epithelial cells, exosomes, and enveloped viruses—are less well understood. Unlike apoptotic cells, activated platelets and T cells are not engulfed by macrophages. The hypothesis that irreversibly exposed PtdSer, rather than reversibly exposed PtdSer, serves as an "eat-me" signal requires further investigation.

Priyanka Narayan - Lipid biology impacts neurodegenerative disease

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Lipids function as both structural and signaling molecules in all cell types. The brain is one of the most lipid-rich organs in the human body. Consequently, disruptions to lipid biology are central to several brain diseases.

Lipid accumulation is a pathological hallmark of common neurodegenerative diseases like late-onset Alzheimer's disease (AD) and Parkinson's disease (PD). Genetic and genomic studies have identified polymorphisms in lipid metabolism genes as strong risk factors for AD (e.g., APOE, PLCG2, ABCA7), PD (e.g., GBA), and other late-onset neurodegenerative diseases. For many years the neurodegeneration field focused on protein aggregate-centric biology. However, we now know that changes to lipid metabolism impact both cell autonomous and cell non-autonomous phenotypes central to neurodegenerative disease biology like amyloid-beta uptake, tau phosphorylation, neuronal communication, lysosomal function, alpha-synuclein aggregation, and microglial inflammation.

Despite the strong genetic and functional associations between lipid metabolism and late-onset neurodegenerative disease risk, the underlying molecular mechanisms remain unresolved. It is an attractive hypothesis that the pleiotropic cellular and systemic effects of neurodegenerative disease risk factors like APOE4 in AD could be consequences of perturbed lipid metabolism. Advances in mass spectrometry-based methodology and cell biology assays to characterize and

target cellular lipid metabolism have enabled the quantitative study of lipid biology in the context of cellular and animal models. Induced pluripotent stem cell-derived tissues allow us to study common and cell type-specific phenomena in human brain cell types.

Now, our challenge is to use these tools to characterize how lipid metabolism is perturbed in different brain cell types in the contexts of neurodegenerative disease risk. We are poised to unearth both the causes and the functional consequences of key lipid metabolic disruptions. And with this knowledge, we can aim to modulate metabolism to mitigate disease risk.

Genetic studies in AD have also identified protective polymorphisms in lipid metabolism genes like APOE and PLGC2. A new frontier in AD research is to understand whether these protective polymorphisms confer resilience to disease by reshaping cellular lipid metabolism. Investigations like these can illuminate protective or preventative strategies for these devastating diseases.

Dequina Nicholas - A Perspective Shift in Immunometabolism from Lipid Metabolism to Lipid Presentation

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Photo credit: Charlie Dunlop School of Biological Sciences

The field of immunometabolism has explored how lipid metabolic pathways influence adaptive immune cell function. However, lipids can also trigger adaptive immune activation through classical mechanisms, including B cell receptor engagement and antigen presentation to T cells. In the 1990s, it was discovered that CD1 molecules (Class I: CD1a,b,c and Class II: CD1d,e) are analogous to Major Histocompatibility Complex (MHC) but present lipids. Despite this discovery, the impact of lipid antigen presentation in human health remains underexplored. CD1d's role in bacterial activation of invariant Natural Killer T cells is an exception.

The absence of literature on this topic is driven by 1) inadequate animal models (mice lack Class I CD1), and 2) technical challenges in measuring lipids in aqueous systems. These challenges prevent exciting questions from being asked, including how the immune system senses dietary lipids and the homeostatic role of adaptive immune responses to endogenous lipids. Immune cell function shifts with diet and even between the fed and fasted state, and it's likely that gut immune cells program systemic lipid metabolism. Transgenic mice expressing Class I CD1, used to demonstrate a role for CD1a in skin inflammation, are a practical model for understanding antigen specific immune responses to dietary lipids. Pigs, which express Class I CD1 molecules and are metabolically similar to humans, are increasingly viable models with an expanding catalog of flow cytometry antibodies.

Finally, advancing the field requires adapting approaches for protein interactions to the study of lipid immune-reactivity. ELISA, flow cytometry and cell sorting rely on aqueous solutions and

soluble antibodies, and thus it is difficult to label cells with lipids that interact with membrane proteins with any degree of certainty or specificity. Interdisciplinary efforts to develop tools to allow identification, isolation, and manipulation of lipid-specific immune cells would create the potential to expand immunometabolism from lipid metabolic pathways to lipid sensing and systemic lipid regulation.

Sara M. Nowinski - Understanding the role of mitochondrial fatty acid synthesis (mtFAS)

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Contrary to their well-known role in fatty acid oxidation (FAO), mitochondria also build fatty acids in the matrix, via the mitochondrial fatty acid synthesis (mtFAS) pathway. mtFAS is essential for oxidative function and well-conserved across species: from yeast, where mtFAS is required for respiratory growth, to mammals, where loss of the pathway is embryonic lethal in mice. The pathway uses acetyl-CoA to build the eight-carbon lipid lipoic acid, a requisite co-factor for mitochondrial dehydrogenases (including pyruvate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase). mtFAS also builds longer FA products, which facilitate physical interactions with the acyl carrier protein on which they are built. These interactions functionally support the iron-sulfur (FeS) cluster biogenesis complex, and several assembly factors for the electron transport chain (ETC). However, the exact identit(ies) and ultimate cellular destination(s) of these longer FA products remain unknown. Moreover, despite recent advances in our understanding of how mtFAS promotes oxidative mitochondrial metabolism, the pathway's regulation, function in diverse tissue settings, and role(s) in disease are largely unexplored.

The evolutionary persistence and essentiality of mtFAS is a teleological mystery. Mitochondria uptake lipids for many other purposes: they import acyl-carnitines for FAO and perform key steps in the biosynthesis and/or metabolism of phospholipids, cholesterol, steroid hormones, coenzyme Q, and Vitamin D. Why then can mitochondria not scavenge abundant mitochondrial fatty acids or exogenous lipoic acid to replace those built de novo by mtFAS? One potential reason is that mtFAS ties many facets of oxidative metabolism (TCA enzyme activity, FeS clusters, ETC assembly) back to the ultimate substrate for catabolism: acetyl-CoA. As a result, the pathway is primarily placed to serve as a central regulatory node in mitochondria, supporting increased oxidative capacity during times of nutrient excess, or coordinating its shut-off when fuels are scarce. This model is supported by data in yeast, where knockout of the mitochondrial pyruvate carrier reduces mtFAS activity but is yet to be demonstrated in mammalian systems. Future studies aimed at understanding how metabolite availability affects pathway activity in mammalian cells will be key to uncovering its role in the nutrient-sensitive regulation of mitochondrial function.

Yasunori Saheki - Control of intracellular lipid distribution via non-vesicular lipid transport at membrane contact sites

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Cells maintain an uneven distribution of membrane lipids across different cellular compartments for their integrity, identity, and functions. While vesicular transport, which relies on membrane budding and fusion, plays a key role in bulk transport of lipids from one compartment to another, this process is often slow and non-selective. Additionally, certain organelles, such as mitochondria and peroxisomes, are not connected to the vesicular transport system, making it insufficient for delivering lipids to these compartments.

Over the years, numerous studies have revealed the critical role of non-vesicular transport in more rapid and selective lipid transport/exchange. In the past decade, our mechanistic understanding of this process has grown exponentially. We now know that non-vesicular transport is often mediated by lipid transfer proteins (LTPs) at membrane contact sites formed between various organelles without membrane fusion, contributing to the control of intracellular lipid distribution. In vitro reconstitution of these reactions, supported by analyses of protein-lipid interactions using structural and biochemical approaches, as well as molecular dynamic simulations, has been instrumental in advancing our understanding of the kinetics of lipid transfer and ligand selectivity of LTPs. Likewise, advanced microscopy techniques, such as high-resolution live-cell imaging and super-resolution microscopy, have provided valuable insights into the cellular localization and dynamics of LTPs at membrane contact sites.

Despite these advances, several critical questions remain unanswered. Further efforts are needed to better understand the importance of non-vesicular lipid transport and its regulation across different cellular and developmental contexts. Investigating the functional redundancy of LTPs, particularly through the use of genetically tractable organisms like *Caenorhabditis elegans* and *Drosophila melanogaster*, is also crucial. Human genetic studies have shown a strong link between the dysfunction of LTPs and various human disorders. However, the physiological impact of LTPs in health and disease is still poorly understood. For example, there is a well-established association between dysregulated lipid homeostasis and neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease. However, we still lack a complete understanding of how LTPs function in neurons and other brain cell types, such as astrocytes, oligodendrocytes, and microglia, to maintain lipid homeostasis in the brain. As we continue to explore the physiological roles of LTPs, it will also be important to develop strategies to manipulate their activities. Such efforts could potentially allow us to harness the lipid transfer properties of LTPs to mitigate the dysregulation of lipid homeostasis in various human disorders, potentially counteracting or even reversing disease progression.

Clay F. Semenkovich - Lipid modification of proteins and disease

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Lipid cell biology, like great art, is associated with a sense of uncertainty. A Jackson Pollock action painting evokes continual motion driven by an uncanny perception of order, resembling the frenetic movement, fusion, and remodeling of organelles and membranes of a live cell. Exocytosis, non-canonical secretion, dynamic functions at membrane contact sites, active transport, and other processes require proteins that adapt to lipid environments that constantly change and differ between subcellular domains. One adaptation is lipid modification of proteins, increasingly recognized as relevant to disease.

S-palmitoylation, the most common form of lipidation, is reversible and affects >10% of human proteins. It involves the addition of palmitate (16:0), the most abundant mammalian fatty acid, to cysteine residues allowing normal intracellular trafficking by promoting membrane association and protein-protein interactions. More than 20 zDHHC acyltransferases create a thioester bond to mark proteins with palmitate (often derived from de novo lipogenesis) and a small group of depalmitoylases (APT1/2, PPT1/2, alpha-beta hydrolase domain enzymes) erase the mark. In multiple tissues, including neurons, endothelial cells, and pancreatic islets, palmitoylation coordinates other posttranslational modifications such as phosphorylation, nitrosylation, acetylation, and ubiquitination. Altered palmitoylation is implicated in neurodegeneration (~50% of synaptic proteins are palmitoylated), vasculopathy (eNOS, R-RAS), diabetes (post-Golgi recycling proteins, mitochondrial proteins), cancer (PD-L1, RAS isoforms, EGFR), inflammatory disorders (STING, Gasdermin, NLRP3 inflammasome), viral infections (SARS-CoV-2 spike protein) and many other diseases.

Given the amazing degree of functional redundancy for marking and erasing palmitate on proteins, we need a better understanding of how palmitoylation is regulated. Do cells use metabolites, phase separation, pH, reactive oxygen species, intracellular calcium, membrane tension, or other factors to alter palmitoylation status? There are substantial sex differences in biological responses of palmitoylated proteins. Does S-palmitoylation underlie sex-based differences in inflammatory disorders such as autoimmunity and atherosclerosis? Palmitoylation detection by current chemical approaches and mass spectrometry is cumbersome, and the generation of antibodies to palmitoylated peptides has been disappointing. New analytical and chemical techniques have the potential to establish mechanistic paradigms to resolve the sense of uncertainty that limits the application of palmitoylation to disease.

Xiaoai Zhao - Uncovering the functional diversity of lipids in aging and diseases

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By way of introduction, lipids are often referred to as one of the "cellular building blocks". As much as it highlights the critical contribution of lipids in biological systems, this depiction does not capture the dynamic functional roles of lipids. Research in the past decades has begun to shed light on the intricate connections between lipid metabolism, aging and diseases. However, the landscape of lipids' contribution in physiology and diseases has only started to emerge. There are a great number of questions and challenges ahead regarding lipids in cell biology, the answers to which could give us insight into targeting lipids as the next frontier in combatting aging and diseases.

Mammals have one of the most complex lipidomes. The chemical diversity of lipid species is been increasingly appreciated, however the implications of what distinct chemical properties can confer in biological processes remains largely unexplored. Phospholipid remodeling enzymes directly contribute to the diversity of phospholipids, by modifying the acyl chain composition of de novo synthesized lipids. Functional studies on this class of enzymes have uncovered the consequences of perturbed lipid side chain composition in pathologies including nonalcoholic fatty liver disease, atherosclerosis, and cancer. Ongoing and future studies aimed at elucidating the mechanistic regulation of lipid composition on their biophysical properties, cell signaling and lipid-protein interactions will provide valuable insight.

At a cellular level, many abundant glycerophospholipid and sphingolipid species can be found in different organelles and compartments across the cell. However, how these lipid classes are regulated in a concerted manner between very different sub-cellular environments is not well understood. For instance, it has been suggested in mouse studies that aging is associated with increased abundance of polyunsaturated fatty acid-containing glycerophospholipids across multiple tissues. But are these composition changes occurring to the same degree in different organelles? If not, what is the role of organelle-specific regulation in shaping the trajectory of aging and diseases? Answers to these questions may guide us toward harnessing the complexity of the mammalian lipidome as a new avenue in understanding the fundamental biology of human aging and diseases.

Yilong Zou - Lipotypes and cancer cell behavior, a systems biology view

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One open question in the field is how the lipidome, together with components of the central dogma, regulates cell identity and behavior. One worthwhile approach is establishing a “lipotype-genotype-phenotype” connection at single-cell resolution. The lipotype can be defined as the collection of cellular lipidome compositions, and the metabolic circuits mediating chemical inter-conversions. Recent advances in multi-omics technologies reinforced the notion that various tissue- and cell-types differ in lipidome compositions, yet the precise contributions of lipidome diversity to cell functions are largely unclear.

In human tumors, malignant clones often exhibit complex behaviors during different stages of disease progression, including proliferation, immune editing and evasion, invasion and metastasis, cell cycle arrest and dormancy, as well as adaptation to therapeutic stress. How does the lipidome support each of these functionalities, and how plastic does the lipidome have to be to support cell-state transitions? For instance, tumor cells surviving in primary carcinomas, ascites, and metastatic sites exhibit different lipidomic profiles, which modulate tumor metastatic potential at multiple steps. We envision systematic characterization of the lipotypes and cancer cell behavior may reveal therapeutically exploitable vulnerabilities in cancer.

Meanwhile, advances in the following technologies will accelerate discoveries: development of sensitive and selective probes that report the physicochemical characteristics of individual and packed lipids, and to be combined with super-resolution imaging to record spatiotemporal dynamics of lipid moieties; single-cell lipidomics and spatial lipidomics at single-cell resolution to report lipidome composition in cells and tissues *in situ*. As an extension, co-detecting lipids, transcripts and/or proteins with spatial coordinates in the same samples will be particularly informative. Furthermore, “functional” single-cell lipidomics, which awaits matured mass spectrometry barcoding strategies to integrate high-throughput genetic perturbations with lipidomics, will accelerate the “correlation” to “causation” transition; as multi-dimensional lipidomics data enrich, machine-learning-based approaches to identify connections between lipotypes and other cellular features will be feasible. Example explorations include identifying lipid groups co-regulated in diverse contexts to uncover principles underlying concerted regulations. Overall, integrating lipid cell biology with system biology tools will help us establish a more holistic view of lipid functions in cell physiology.