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Lipid homeostasis and regulated cell death

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Modern lipidomics analysis paints a dynamic picture of membrane organizations, as changing and adapting lipid assemblies that play an active role in cellular function. This article highlights how the lipid composition of membranes determines specific organelle functions, how homeostatic mechanisms maintain these functions by regulating physical properties of membranes, and how cells disrupt lipid homeostasis to bring about regulated cell death (RCD). These are broad phenomena, and representative examples are reviewed here. In particular, the mechanisms of ferroptosis – a form of RCD brought about by lipid peroxidation – are highlighted, demonstrating how lipid metabolism drives cells' lipid composition toward states of increased sensitivity to lipid oxidation. An understanding of these interactions has begun to give rise to lipid-based therapies. This article reviews current successes of such therapies, and suggests directions for future developments.

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Introduction

Lipidomics analyses have transformed our understanding of cell membranes, from the more static conceptualization of the fluid mosaic model [1], to a more complex conceptualization in which different stable and transient microdomains coexist in the same membrane [2•,3,4]. Compositions are continuously remodeled through regulatory metabolic processes, and networks of lipid sensors and pipelines traffic membranes between organelles. Organelle membrane compositions are fine-tuned by homeostatic mechanisms to fit their required function, whether acting as barriers, regulating permeation, facilitating signal transduction, trafficking membranes, or storing energy. These in turn contribute to cellular viability by maintaining properties such as ionic and redox homeostasis, and protein function.

In turn, membranes are increasingly recognized as parts of complex mechanisms that regulate growth, development, and cellular homeostasis — mechanisms that, when altered, can lead to membrane degradation, cellular dysfunction, and ultimately cell death (Figure 1). By understanding lipid organization and dynamics more completely, we gain a deeper appreciation for lipids' role in cell biology and in disease. With this knowledge, researchers have come to control cellular dysfunction with new types of lipid-based therapies that target organelles based on their lipid compositions. This article outlines these developments.

Lipidomics methods

Lipidomics is the systems-level analysis of lipids and their interactions [5•,6•], with the aim of characterizing the lipidome — the full set of lipids in each cell, and their dynamics. Modern lipidomics consists of several experimental techniques in which lipids are isolated from cells or tissues, separated into different lipid species, and analyzed to obtain a global profile of lipids present and their relative abundances [7].

Analysis

While there have been advances in NMR spectroscopy [8] and novel approaches to lipidomics analyses [5•], high-performance liquid chromatography (HPLC) and mass spectrometry have emerged as the primary approaches for lipidomics [9]. Advances in mass spectrometry methods, such as electrospray ionization (ESI), matrix-assisted laser desorption/ionization (MALDI), and tandem mass spectrometry (MS/MS), overcame earlier problems in studies with fast-atom bombardment and chemical ionizations [10,11]. These methods allow for the simultaneous analysis of complex mixtures of lipids, and high-throughput profiling of lipids from small samples.

After data acquisition, the results are processed using bioinformatics tools, which perform peak detection, peak alignment, and peak matching, and identify how peaks change between samples [7,12]. There are new lipidomics databases, such as LIPID MAPs, which provide classification systems for lipids and increase the range of lipid classes that are represented [13]. Such databases have enabled researchers to quantify known lipid species, and search for novel lipids more effectively.

Furthermore, such systems allow for the quantification of lipid species based in their absolute abundance, as opposed to relative changes.

These approaches allow for profiling of lipid extracts, which can identify lipid metabolic pathways and enzymes that are affected by perturbations. High-throughput screening of compounds can also target lipid pathways and determine functional consequences on cellular viability.

Computational lipidomics

Computational methods, such as molecular dynamics, can simulate lipid compositions to predict their interactions and physical properties [14,15•]. Such simulations provide an understanding of how lipid profiles of various membranes generate macroscopic properties that are relevant at the cellular level. For example, simulations of heterogeneous lipid membranes reveal phase behavior, including fluid and disordered, rigid and ordered, fluid and ordered [16]. Furthermore, simulations reveal that there are membrane compositions in which multiple phases coexist — a phenomenon that has been examined with lipidomics following the discovery of lipid rafts [2•,4,17].

Membrane composition and function

Eukaryotic cells have thousands of lipid species in each cell; these are classified into several major categories, including fatty acids (FAs), glycerophospholipids (GP), glycerolipids (GL), sphingolipids (SP), prenol lipids (PR), and sterol lipids (ST) [18,19]. These lipid species are further divided into subclasses, each with a diverse set of molecular structures, and each contributing unique functional properties when combined in lipid membranes.

Lipid distributions are heterogeneous across intracellular organelles (Figure 1c), across microdomains within membranes [20•], and across the inner and outer leaflets of bilayers. Distributions are determined both by local lipid metabolism occurring in each organelle, and by lipid trafficking between organelles. Lipid compositions are dynamic, with daily oscillations in organelle membranes [21], high lipid trafficking between organelles [22•,23••], and sensitivity to environmental conditions [24].

Each organelle's membrane serves a different function, and needs to maintain its physical properties within a different range. For example, the endoplasmic reticulum (ER) needs to be more fluid to facilitate membrane trafficking, and the plasma membrane needs to be more rigid to support its barrier function. These properties are in part determined by the composition of FAs: FAs with shorter chains are more fluid because they have less surface area for stabilizing non-covalent interactions, and unsaturated FAs – monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs) – are more fluid than saturated FAs because the kink in their tails makes them harder to pack together. Because of this, the ER has more unsaturated Fas, which create a thinner membrane with increased fluidity and reduced surface charge, and the plasma membrane has more saturated FAs and STs which increases membrane thickness, increases surface charge, and increases rigidity [23••].

The particular composition of a membrane can alter protein function, both by determining the location of proteins, and by directly influencing their conformation [25]. Membrane fluidity promotes an increased rate of protein–protein interactions. Additionally, microdomains, known as lipid rafts, that are rich in SP and cholesterol, create rigid aggregations that concentrate select proteins, and create platforms for cell signaling, cell adhesion, and protein sorting [4,17]. Lipids also directly influence the post-translational modification of proteins [26•]; lipid functional groups attach to proteins by specific transferases, and modify distinct properties of the protein. Most commonly, the outcome of lipid modification is an increased affinity for membranes, but it can also promote protein–protein interactions. Lipid signals bind to protein target, and are qualitatively different from other signaling paradigms because lipids can freely diffuse through membranes.

Lipid homeostasis

Membranes properties, and therefore functions, are fine-tuned by complex homeostatic mechanisms, and are in turn part of the complex machinery that maintains cellular and organismic homeostasis. Each physical property needs to be maintained within a range, and often with one property influencing the others. Thus, membrane properties need to be carefully balanced, but are sometimes at odds with each other. Understanding the principles underlying these mechanisms and their interrelations provides an avenue for controlling cell properties through the manipulation of lipid compositions.

Membrane homeostasis

Membrane function is tightly regulated by mechanisms that modify lipid composition. This includes regulation by biosynthesis and regulation by lipid trafficking. Biosynthesis of lipids is partially determined by lipid-composition sensors that upregulate or downregulate the activity of lipid enzymes according to properties of lipid composition [27•,28,29]. For example, membranes regulate their fluidity in response to the environment through embedded thermosensors [24]. Membrane tension is kept stable through the physical feedback of membrane bending energy, which alters the conformation of a membrane-embedded enzyme, phosphocholine cytidylyltransferase [29]. Caveolae – small cup-shaped membrane invaginations rich in sphingolipids and cholesterol – have also been shown to act as mechanosensors and mechanotransducers that regulate membrane tension through their disassembly/reassembly cycles [30,31]. Additionally, lipid composition is maintained by membrane trafficking between organelles; this is determined by networks of