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Lipid homeostasis and regulated cell death

Eran Agmon[1] and Brent R Stockwell[1,2]

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.

Addresses
[1] Department of Biological Sciences, Columbia University, 550 West 120th Street, MC 4846, New York, NY 10027, United States
[2] Department of Chemistry, Columbia University, 550 West 120th Street, MC 4846, New York, NY 10027, United States

Corresponding author: Stockwell, Brent R (bstockwell@columbia.edu)

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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

diffusing lipid droplets operated by lipid transfer proteins (LTPs) [23••,32], or through direct exchange at membrane contact sites between organelles, in which LTPs shuttle lipids from one organelle to another [33]. The ER plays a central role in lipid trafficking, as the primary secretory organelle and exchange network that moves lipids between organelles. Transfer proteins are highly selective in their transport of lipids, with many unidirectional transfers between organelles allowing cells to maintain highly inhomogeneous distributions of lipids.

Membranes maintain ionic homeostasis — the stable ion gradient that allows ions to continuously move across the membrane and drive ongoing reactions and signals [34]. Ionic homeostasis is tied to osmotic homeostasis — the pressure difference and the concentrations of ions in cell's water content. These properties are controlled both by active and passive transport of ions across the membrane, determined by membrane permeability and embedded transport proteins. The net flow determines a cell's volume and internal pressure, and it also allows for charge differential across the membrane, as required by mitochondria for respiration and by nerve cells for maintaining a resting potential. When ionic homeostasis is disrupted, cell signaling and transport are compromised. When osmotic homeostasis is disrupted, cells shrivel or burst.

Redox homeostasis

Lipid composition plays a role in redox homeostasis — the balance of oxidative and reducing reactions present in all living systems [35,36••]. Reactive oxygen species (ROS) are common redox signals produced by the mitochondria, and are usually tightly regulated. ROS include lipid peroxides (L-OOH), which are produced by lipoxygenase enzymes and as byproducts of NADPH oxidases, as well as through non-enzymatic processes. L-OOH are stable, diffuse in membranes, and can serve as lipid signals [37]. Their physical properties alter membrane characteristics, such as lipid–lipid interactions, ion gradients, decreased membrane fluidity, and increased membrane permeability. These changes to membrane properties influence the post-translational modification of proteins [37].

Despite their relative stability, L-OOH are prone to degradation into reactive compounds that self-propagate, forming more ROS that disrupt metabolic processes, DNA, and proteins. Such imbalances in lipid peroxide abundance have been linked to pathological conditions such as inflammation, cancer, Alzheimer's, and other degenerative diseases. To avoid these adverse effects, cells possess mechanisms to eliminate harmful peroxides, and maintain redox balance. Glutathione peroxidase (GPx) enzymes, particularly GPx4, are key enzyme that counters peroxidation by reducing L-OOH to lipid alcohols (L-OH), with glutathione (GSH) as a co-substrate [38].

Lipids in regulated cell death

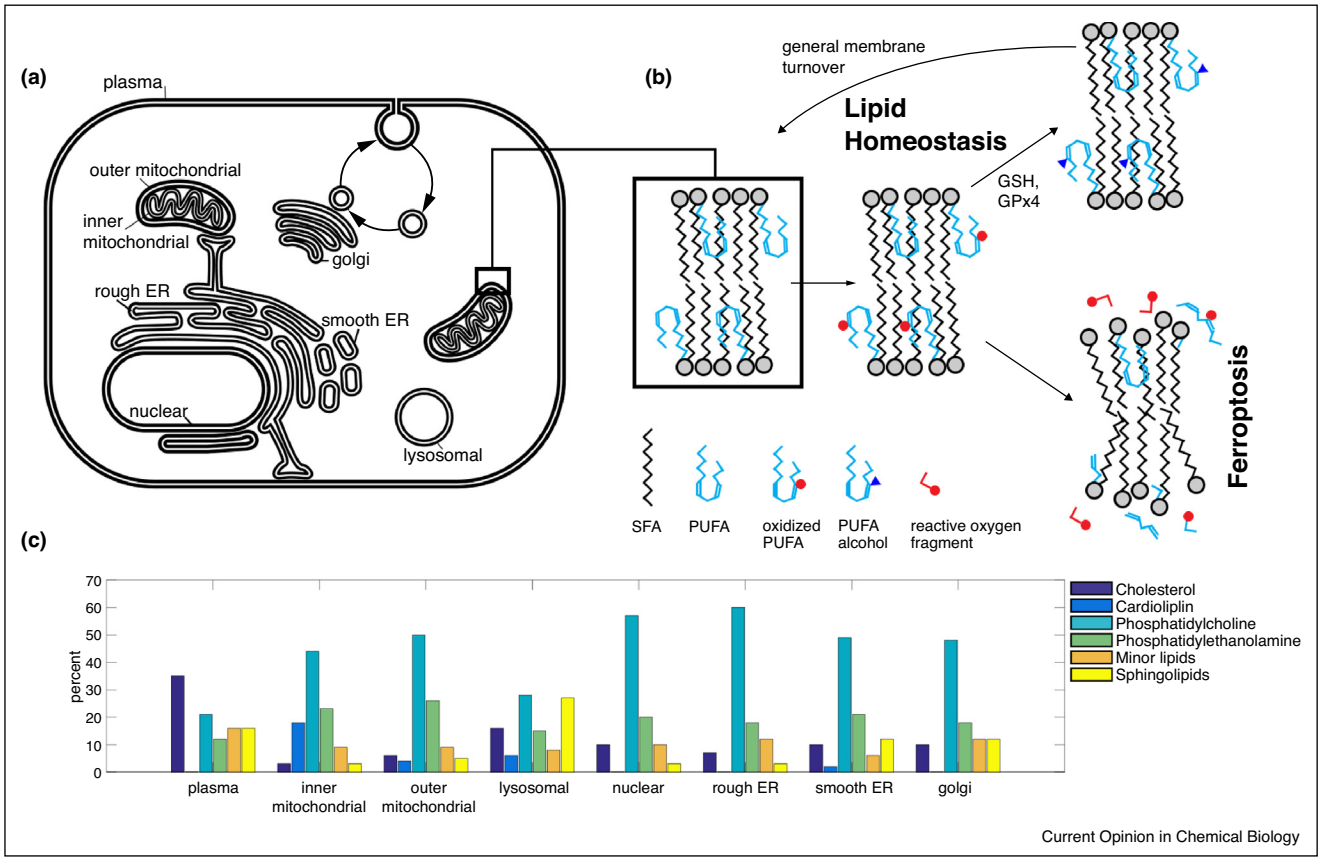
There are several forms of regulated cell death (RCD) that use lipids as key parts of cell death pathways, either as initiators of cell death, mediators of cell death, or as key targets for modification and destruction [39••]. These include apoptosis, necroptosis, and ferroptosis, which navigate cells to death in a controlled manner through separate biological pathways. Figure 2 highlights the role of lipids in these three forms of RCD. Apoptosis is mediated by a group of caspases that cleave proteins, cause DNA to break apart, form an ion channel in the outer mitochondrial membrane, and ultimately lead to the dissolution of cells into smaller bodies. Necroptosis is a necrotic cell death, independent of caspase activity, in which the cell plasma membrane ruptures. Ferroptosis is an iron-dependent form of cell death caused by the accumulation of lipid peroxides.

Lipids are involved in all stages of apoptosis [39••]. The FA palmitate acts as a signal that initiates apoptosis by triggering an ER stress response, while ceramide transduces this signal. Sphingolipids (SP) act as mediators by oligomerizing pore-forming proteins, BAK/BAX, on the mitochondrial outer membrane. The mitochondrial outer membrane is a target for apoptosis pathways, and its permeabilization drives death [40]. Mitochondria exchange lipids with the ER membrane to actively remodel the sphingolipid and cardiolipin (CL) composition that promotes apoptosis [41•]. With the onset of apoptosis, lipid flippases and scramblases increase concentrations of the phospholipid phosphatidylserine (PS) on the outer plasma membrane, which provides a signal for recognition of apoptotic cells by external phagocytes.

Necroptosis requires a direct interaction between membrane lipids and the mixed lineage kinase domain-like protein (MLKL) [42]. At the end of a complex regulatory pathway, MLKL is phosphorylated by receptor interacting protein kinase 3 (RIPK3), and then phosphorylated MLKL oligomerizes to form MLKL complexes, which are translocated to lipid rafts in the plasma membrane. MLKL binds to membrane phosphatidylinositol phosphate (PIP) lipids, which opens a pore that causes membrane leakage and loss of ionic homeostasis

Ferroptosis is characterized by the accumulation of oxidized PUFAs. Cells are driven to ferroptosis by finely regulated lipid metabolism pathways to increase sensitivity to PUFA oxygenation. There are a several pathways that control this process, all involving the inhibition of GPx4 or depletion of GSH, which due to the mechanisms described in Section 'Redox homeostasis', results in the accumulation of lipid peroxides. This accumulation may lead to cell death in several ways: 1) membrane destruction and the opening of pores leading to loss of ionic homeostasis, 2) membrane compositional changes that alter embedded protein

Figure 1



Summary of lipid homeostasis and regulated cell death. **(a)** Several lipid membranes in a cell are shown. These include the plasma membrane, inner mitochondrial membrane, outer mitochondrial membrane, lysosomal membrane, nuclear membrane, rough endoplasmic reticulum, smooth endoplasmic reticulum, and golgi membranes. Each organelle facilitates different lipid metabolism pathways, and thus alters local lipid composition. Lipid trafficking is depicted by membrane contact sites and vesicular traffic. **(b)** Lipid homeostasis maintains stable lipid composition, and its disruption leads to cell death. Peroxidized polyunsaturated fatty acids (ox-PUFAs) – shown with red dots – are reduced to lipid alcohols by glutathione peroxidase (GPx4) with glutathione (GSH) as a substrate, and this facilitates a stable ongoing lipid turnover (top branching arrow). The inhibition of GPx4 allows for the accumulation of ox-PUFAs, leading to cell death by ferroptosis (bottom branching arrow). **(c)** The lipid compositions of several organelles.

interactions, or 3) oxidized PUFAs fragment, releasing ROS that interfere with other cellular processes.

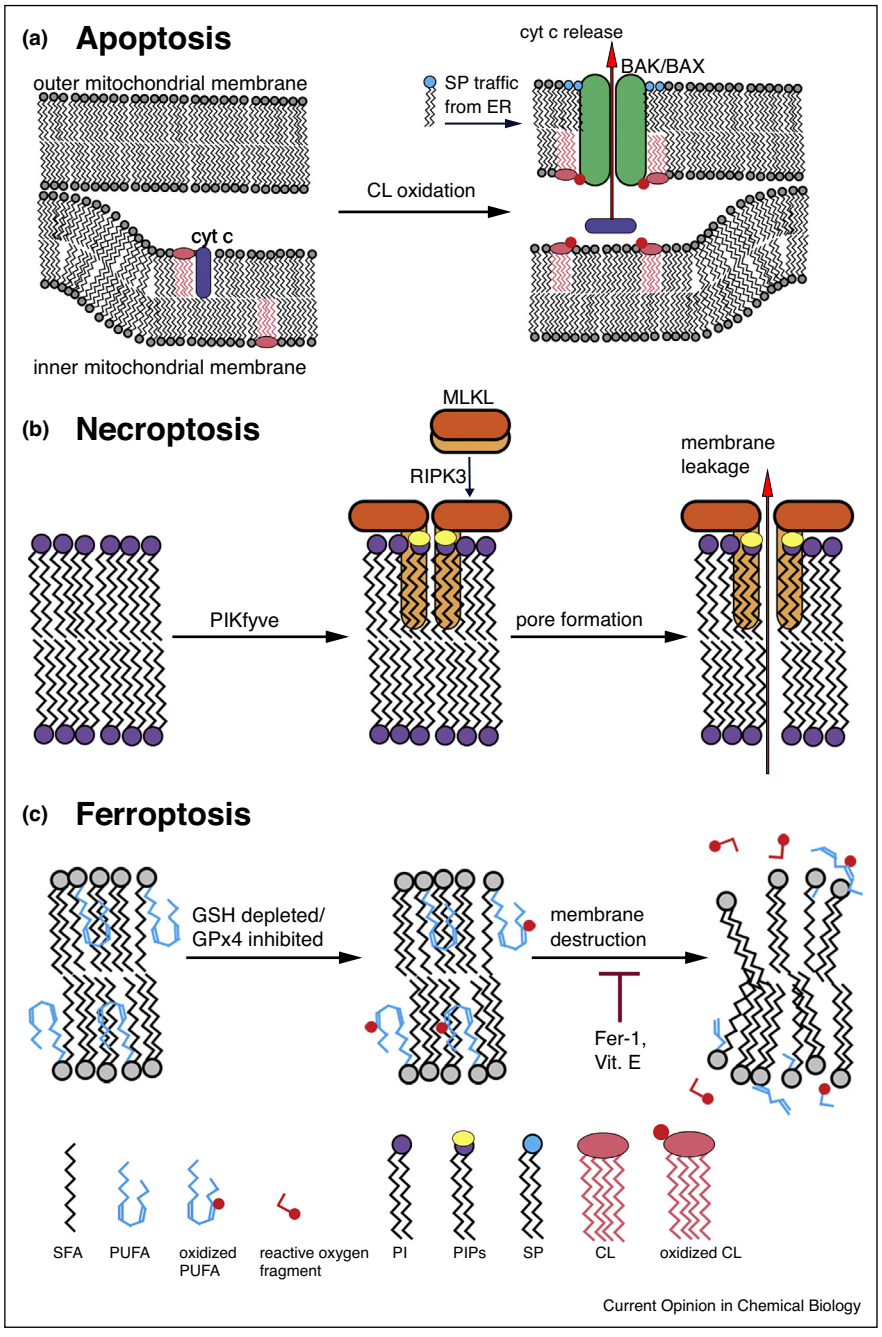
Fatty acid synthesis and the mevalonate pathway both regulate sensitivity to ferroptosis through distinct mechanisms [43]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) dictates ferroptosis sensitivity by shaping lipid compositions [44•,45•] — it incorporates long PUFAs into membranes, and thus increases the rate of ferroptosis. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) inserts an acyl group into lysophospholipid (which only have one FA tail), specific toward the phospholipids phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [46•,45•].

The metabolic changes of ferroptosis lead to specific morphological changes in the lipid properties of two organelles: the mitochondria and ER. Mitochondria become shrunken, with membranes that are much denser, electron-dense, with reduced cristae, and outer membrane rupture [47]. ER compartments show highly organized oxygenation centers on one class of PE, and is specific toward arachidonic and adrenic FA tails [46•]. The accumulation of these specific oxidized phospholipids steers cells toward ferroptosis.

Lipid membrane therapies

Lipid membrane therapy is an approach for treating disease by modifying the membrane compositions of cells [48••]. Membranes can be altered in several ways, including (1) directly changing the lipid composition through diet or other interventions, (2) regulating enzyme activity to alter lipid composition, or (3) modulating gene expression that alters lipid composition. Membrane lipids offer novel drug

Figure 2



The role of lipids in three forms of regulated cell death. **(a)** Apoptosis involves lipids at many stages. Sphingolipid (SP) traffic from the ER promotes the activation of BCL2-associated X (BAX) and BCL2-antagonist/killer (BAK). When cardiolipin (CL) is oxidized, protein cytochrome c (cyt c) is released from the inner mitochondrial membrane through BAK/BAX in the outer mitochondrial membrane. **(b)** Necroptosis requires RIPK3 to phosphorylate MLKL, which oligomerizes to form MLKL complexes. These complexes translocate to lipid rafts in the plasma membrane, bind to phosphatidylinositol phosphate (PIP) lipids, and open a pore that causes membrane leakage. **(c)** Ferroptosis is driven by the accumulation of oxidized PUFAs, which result from the depletion of GSH or inhibition of GPX4 — a lipid repair enzyme. Ferrostatin-1 (Fer-1) or vitamin E can inhibit the destruction of the oxidized membrane, but in their absence the membrane is destroyed and toxic reactive oxygen fragments are released into the cell (panels b and c adapted from Ref. [39••]).

targets, and new sets of drug candidates and methods of drug delivery. Such therapies have been developed in oncology, obesity, diabetes, hypertension, Alzheimer's disease, and other neurological disorders.

Membrane-embedded proteins make up the majority of known drug targets; this suggests that one can target membranes for their influence on proteins. Membrane compositions influence protein conformation, protein

localization, and protein–protein interactions (as described in Section 'Membrane composition and function'). In particular, lipid raft microdomains are known to aggregate signal proteins [4,17] (such as G proteins and protein kinase C [48••]), and rafts' binding affinity to these proteins can influence signal transduction [49]. Altered membrane composition can therefore be used to target specific proteins' structure, behavior, and interactions.

Lipids and genes also co-regulate each other, which provides a means for therapies to target genes by way of lipids, and for control of lipid-related gene expression. Phospholipids exist within cell nuclei, and play a regulatory role [50], suggesting that lipid signals can be used to influence gene expression. Researchers have developed synthetic ligands that alter gene expression and influence the FA composition of phospholipids in mice [51]. These enzymes can desaturate and elongate FAs, causing significant increase in MUFA within membrane phospholipids.

Lipid-dependent RCD mechanisms also offer promising pathways for future therapies. By altering lipid composition to induce or suppress RCD in specific tissues, pathological conditions might be controlled. Targeted metabolomics has uncovered two ferroptosis inducers that prevent tumor growth in mouse tumor models [38]. The role of ferroptosis in various disease has been evaluated using ferrostatin-1 (fer-1), a small-molecule inhibitor of ferroptosis [52••], and liproxstatin [53]. An emerging strategy to prevent lipid peroxidation is supplementation with fatty acids labeled deuterium at sites prone to oxidation [36••,54•].

In addition, lipid-based nanoparticles provide a promising route for drug delivery [55]. Liposomes are vesicles of phospholipids that enclose a water droplet, which are often used by cells for the transportation of nutrients. An understanding of liposomes' membrane properties and their resulting interactions within the cell can inform the design of a lipid-based nanoparticle that can carry drugs directly to DNA or other targets. Such lipid-based nanoparticles are the least toxic of many currently explored nanoparticle delivery systems, due to lipids' ability to form stable compartments, diffuse freely within a cell yet be selectively trafficked to organelles, and open up pores through slight alterations of composition.

Discussion

Modern lipidomics studies reveal the intricate dynamics of cells' lipid membranes. They are complex structures, with widely differing compositions across the intracellular membranes, plasma membrane, and microdomains, whose compositions determine a wide range of physical properties, and are intricately tied to cellular function and homeostasis. These boundaries of and within cells are the sites of many cellular functions, such as signaling, transport, and maintaining essential gradients. Altering lipid composition at these sites can lead to the disruption of lipid homeostasis, disruption of cellular homeostasis, and cell death. Indeed, dysfunction of lipid homeostasis is tied with many pathological and disease states.

Researchers have uncovered new pathways for regulating cell function, such as enhancing or suppressing cell death mechanisms, by focusing on the composition and physical properties of lipid membranes, how they are regulated, and how they in turn regulate essential homeostatic states of cells. Membrane-embedded proteins make up the majority of current drug targets, and these proteins are regulated by lipid composition and can be targeted through lipid pathways. Thus, a deeper understanding of membrane lipid properties and dynamics is opening up entire new avenues for drug discovery, and can revolutionize our understanding of lipid biology.

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