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Biochimie 215 (2023) 1-3. Editorial for the Special issue “Lipids - from Membrane Dynamics to Signaling”

Lipids play music at the cellular membrane: from membrane dynamics to signaling via lipid mediators, vesicles and lipid droplets

The front cover for this special issue is a metaphoric representation of lipid science that takes place at the cellular membrane. By their molecular diversity, lipids can self-organize into membranes from which many biological functions can emerge in a dynamic way, including the production of lipid droplets (LDs) for the storage and subsequent delivery of energy or for their later conversion into milk fat globules (MFGs), the production of lipoproteins (such as LDLs) or the release of extracellular vesicles (exosomes, etc). Last but not least, membrane lipids are used by multiple enzymes for the production of potent lipid mediators (LMs) that are involved in a myriad of physiological and pathophysiological conditions. Lipids are therefore essential for writing the musical score of life. To illustrate the ongoing research in this continuously evolving area, this special issue assembles a collection of original articles and reviews of some of the lipid science that was presented at the 17th GERLI Lipidomics meeting, entitled “LIPIDS: from membrane dynamics to signaling”, which was held in Saint-Jean-Cap-Ferrat, France, on November 6-9, 2022. The meeting gathered researchers from various areas, who discussed cutting-edge research on lipid membrane components and lipid remodeling, mechanisms linking lipid membrane dynamics to lipid mediator signaling, up to lipid functions in physiology, pathophysiology and applications in nutrition and health, as well as in diagnosis and therapy of lipid-driven diseases.

One well-known but intriguing LD is the milk fat globule (MFG). It has the particularity to be exclusively secreted from mammary gland epithelial cells. After migration to the apical pole of the cell, the “LD-MFG” docks to the plasma membrane and exits the cell covered by a double lipid layer by a mechanism which may be analogous to pinocytosis but in the reverse direction. The resulting milk fat globule membrane (MFGM) is thus composed of three lipid layers in which various proteins originating from the original LD and the plasma membrane are embedded. The review by Tzirkel-Hancock et al [1] describes this mechanism and the various factors including cellular stress that influence the size and composition of the MFG, and how this can exert an adaptive benefit to the lactating mother or the infant.

Some lipases are active on both triglycerides and polar lipids, and they are important enzymes for the release of fatty acids and remodeling of cellular membranes [2]. Among them, pancreatic lipase related-protein 2 (PLRP2) displays both phospholipase A1 and galactolipase activities, the latter being associated with the digestion of plant photosynthetic membranes [3]. Kergomard et al. [4] used mixed Langmuir monolayers containing galactolipids, phospholipids and phytosterols as plant membrane model systems to investigate how the lipid composition and phase heterogeneity within the membrane can impact the enzyme adsorption and activity. Surface tensiometry, ellipsometry and atomic force microscopy after Langmuir-Blodgett transfer are used to reveal the phase heterogeneity and monitor enzyme kinetics.

The review by Valentine et al. [5] describes the importance of lysophospholipid acyltransferases (LPLATs) in the remodeling of membrane phospholipids. This review reports a concise update on the 14 LPLAT members, which are conserved in mice and humans. It highlights the novel nomenclature of LPLATs (1-14) putting together the AGPAT (1-acylglycerol-3-phosphate *O*-acyltransferase) and MBOAT (membrane bound *O*-acyltransferase) families and reviewing their pathophysiological roles.

The review by Takeshi Harayama [6] highlights the importance of various cellular phospholipids in regards to their chemical structures and association to different metabolic

pathways. The review focused on a phenomenon named for the first time by Takeshi Harayama: “structure-guided metabolic bias”, which is well described and discussed in terms of biological relevance.

Lipid biosensors are useful tools to visualize and quantify specific lipid species in live cells. The article by Eisenreichová et al [7] focuses on the impact of membrane properties, such as fluidity and membrane charge, on the sensitivity of two widely used lipid biosensors, LactC2 and P4M, to their target lipids, PS or PI4P, respectively. Using dual-color fluorescence cross-correlation spectroscopy, they investigated the binding properties of these biosensors to liposomes of various lipid compositions with high sensitivity. They found that LactC2 has limited efficacy in detecting low levels of PS in simple lipid mixtures consisting of POPC/POPS. The presence of other anionic lipids in these membranes significantly improves the detection of PS. Comparable experiments for P4M revealed that this PI4P probe is less sensitive to the membrane environment. The presented results raise concerns about the quantification of sensed lipids based on biosensor abundance and highlight the importance of understanding the behavior and limitations of lipid biosensors in the context of the lipid membrane environment.

Ether-lipids (ELs) are specific lipids bearing a characteristic *sn-1* ether bond. Alkyl- and alkenyl-ELs differ by the ether or vinyl-ether nature of this bond. The review by Papin et al. [8] summarizes the roles and mechanisms of action of ELs in cellular signaling, trying to discriminate between alkyl- and alkenyl-ELs. Alkenyl-ELs, which are also referred as plasmalogens, have attracted most of the scientific interest as they are the predominant EL species in eukaryotic cells, while much less is known about alkyl-ELs. ELs have been implicated in various signaling pathways, with amounts altered in pathologies such as cancers or neurodegenerative and cardiovascular diseases. However, it remains unknown whether both alkyl- and alkenyl-ELs play the same roles in these processes. The review also focuses on the

involvement of EL-mediated alterations of cellular signaling in diseases and discusses the potential interest of ELs in therapy.

Leukotriene B₄ (LTB₄) is a lipid mediator generated from arachidonic acid in response to various stimuli. This important lipid exerts its biological activities by binding to two LTB₄ receptors: BLT1 and BLT2 which are high and low affinity receptors, respectively. The review by Nakamura et al. [9] focuses on the biosynthesis and biological roles of LTB₄ through its two receptors. They describe the effects of receptor deficiencies in pathophysiological conditions, up to the potential of LTB₄ receptors as therapeutic targets. Moreover, the current information on the structure and post-translational modifications of BLT1 and BLT2 is discussed. In various diseases, the pathophysiological importance of LTB₄ and their receptors have been clarified. For example, disruption of the BLT1 gene or the use of receptor antagonists reduced disease activity in rheumatoid arthritis and bronchial asthma. In contrast, BLT2 deficiency facilitated several diseases in small intestine and skin. The data suggest that BLT1 blockers and BLT2 agonists could be useful in therapy. Drugs targeting each receptor are being developed by pharmaceutical companies.

Non-Alcoholic Fatty Liver Disease (NAFLD) is classified as a pandemic disease, with no effective treatment available so far. The review by Teixeira et al. [10] evaluates our current understanding on the onset, progression, and prevention of NAFLD through the analysis of plasma and liver lipidome. Several biomarkers are discussed among which lipid droplets are highlighted as dynamic organelles that represent potential targets for therapeutic intervention.

Epidermal lipids play important roles in skin homeostasis and diseases. Psoriasis is an inflammatory disease characterized by keratinocyte hyperproliferation and Th17 immune responses. Yamamoto et al. previously reported that ethanolamine-type lysoplasmalogen (P-LPE), preferentially produced by the group IIF secreted PLA₂ (sPLA₂-IIF/PLA₂G2F) that is expressed in the suprabasal epidermis, promotes epidermal hyperplasia in psoriatic inflammation [11]. In this original article [12], Yamamoto et al. further show that the forcible

degradation of epidermal P-LPE by topical application of recombinant lysophospholipase D (LyPLs-PLD) from *Thermocrispum*, a lysoplasmalogen-specific hydrolase, attenuated epidermal hyperplasia and inflammation in imiquimod-induced and K5.Stat3C transgenic mouse models of psoriasis. In humans, P-LPE levels are elevated in the tape-stripped stratum corneum of patients with psoriasis. Moreover, in primary cultured human epidermal keratinocytes, the aberrant cell proliferation and activation induced by psoriatic cytokines were sPLA2-IIIF/P-LPE-dependent and suppressed by addition of LyPLs-PLD. The findings confirm the importance of the sPLA2-IIIF/P-LPE axis in psoriasis, and may lead to the development of new therapeutic and diagnostic applications.

Bacteria are rich in lipids with a high diversity, belonging to several lipid families and characterized by different stereospecific isomeric structures. The review by Fong-Fu Hsu [13] describes an updated method to elucidate the structure of complex bacterial lipids. Modern mass spectrometry plays an important role, thanks to the continuous improvement of sensitivity and speed of analysis, gaining more complete structural information. This review focuses on the description and use of linear ion trap multiple-stage mass spectrometry with high resolution instruments leading to a more complete structural identification of native bacterial lipids. Several examples are discussed for complex and rare lipids, including those consisting of stereoisomers.

The review by Gaudu et al. [14] explores the interaction of minerals with liposomes. Mineral-liposome hybrid systems currently present interesting applications in the medical field for diagnosis and targeted therapeutics. They can be used for targeting, controlling and improving drug delivery by liposomes [15]. Iron-oxide nanoparticles, such as magnetite (Fe₃O₄)-embedded liposomes, are used as contrast agents in magnetic resonance imaging (MRI), as well as in targeting of tumors [16]. They enable payload release near the tumors in response to specific stimuli such as electromagnetic heating, magnetic field or photothermal activation [17]. Besides such medical applications, they can be used as models for the

emergence of life on earth. Indeed, minerals may be key elements used as inorganic catalysts in the formation and energetic sustaining of the first cell-like biological systems [18].

To conclude, this special issue assembles several reviews and original articles that each exemplify the multiple roles of lipids, playing a ‘‘symphonic concerto’’ at the cell membrane. This concerto transitions from membrane dynamics to lipid signaling, including phospholipid remodeling and the role of lipids as building blocks, their role in the formation of lipid droplets, milk fat globules or other vesicles, their conversion into potent lipid mediators by multiple signaling pathways, and their utilization in nanolipid biotechnology for improved medicine. Nature may have orchestrated lipids at the cellular membrane to bring together the essential elements of life, like a musician can write the key musical notes for a lovely song.

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