Biochimica et Biophysica Acta 1838 (2014) 1449–1450

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Preface

Membrane structure and function: Relevance of lipid and protein structures in cellular physiology, pathology and therapy

Membranes form selective barriers that separate, communicate and define cells and their internal organelles, and they also receive and propagate important signals that control cellular behavior. It is conventional wisdom that most of the activity of a cell occurs within or around membranes, and in this context, the functions of membranes do not depend exclusively on the particular proteins that they contain, but rather, they also depend on lipid composition and the lipid–protein structures of membranes. These features of membranes both influence and participate in the specific functions associated with different cells and the overall control of a cell's physiology.

Importantly, alterations to the membranes of a cell may be involved in various pathological processes. In this respect, interventions aimed at regulating membrane composition, such as the replacement of damaged phospholipids or the regulation of the membrane lipid composition, constitute an innovative form of treatment (lipid replacement therapy or membrane lipid therapy). This special issue of BBA Biomembranes aims to reflect the current status of this field, placing particular attention on the most recent advances in membrane structure, composition and dynamics, especially membrane lipids, as well as their modifications by therapeutic intervention. As such, this issue will be an important contribution to a field that is of utmost importance in biology and medicine.

Our knowledge of membrane structure has been acquired over approximately the last century, developing from the initial discovery that cell membranes contained lipids that could account for some of their biophysical properties. It was almost 90 years ago that Gorter and Grendel first proposed that cell membranes were formed by a lipid bilayer [1]. Subsequently, Davson, Danielli and Robertson proposed trilayer membrane models that contemplated a complex organization of membranes, with protein layers surrounding a lipid bilayer [2,3]. An alternative membrane structure was also proposed based on repeating lipoprotein subunits without a supporting lipid bilayer matrix [4,5]. These models represented the first approaches that considered membrane structure and function from a new perspective, although they still did not take into account membrane dynamics. The first model to consider the mobility of membrane components in the plane of the membrane, the fluid mosaic membrane model, depicted biological membranes as a fluid bilayer of phospholipids into which mobile globular integral membrane proteins and glycoproteins were intercalated [6]. This model contemplated dynamic changes in the organization and mobility of lipids and integral and peripheral membrane proteins. Indeed, this model is still valid, especially at the nano-scale level, if we accept certain modifications, and it still constitutes the basic platform for many new concepts related to the structure and function of biological membranes.

The plasma membrane's relationship with the cytoskeleton and the presence of membrane microdomains that define specific “plasma membrane compartments” were initially described in the 1970s [7–9]. Furthermore, during the 1980s the importance of the lipid environment in the function of transmembrane proteins began to be deciphered [10–12]. By the 1990s, the roles of membrane lipid composition and structure and how they influenced the localization, mobility and activity of relevant peripheral membrane proteins, such as G proteins and PKC, were revealed, highlighting the importance of membrane structure and dynamics in the control of cellular signaling [13–15].

More recently, the physical properties of membranes that determine their structure and function have become an important area of research [16,17]. In addition, the finding that some lipid alterations are associated with cellular pathologies is a further indication that membranes are more than just a physical boundary defining cells and organelles. Significantly, the expansion in our understanding of membrane structure and function has enabled nutraceutical and pharmaceutical interventions to be developed that target certain membrane components, such as the lipid bilayer [18,19].

This special issue contains a number of reviews that will provide the reader with an insight into our current understanding of cellular membranes, especially membrane lipid structures, and functions and their potential therapeutic manipulations. . To begin with, two authoritative opinions and updates of the fluid mosaic model of membrane structure have been contributed by Garth Nicolson and Félix Goñi, and a further three reviews deal with specific issues related to membrane lipid composition. Dennis E. Vance has reviewed the phosphatidylethanolamine N-methyl transferases and how they influence the physiological membrane lipid composition, as well as their participation in pathological alterations of the membrane. In addition, Guschina et al. have addressed important aspects of lipid biosynthesis in plants, while D'Souza and Epand highlighted the roles of phosphatidylinositol molecules with specific fatty acyl moieties. The studies by Ibarguren et al., Piotto et al., and Tsai et al., each focus on specific structural aspects of the lipid bilayer, such as the effect of fatty acids on the membrane structure and the role of lipids in the multi-step process of membrane fusion.

Protein–lipid interactions have crucial effects on the function of membranes, and in this context, Philip Yeagle has reviewed the specific interactions of the most important membrane lipids with a wide variety of membrane proteins. The article by López-Rodriguez and Pérez-Gil highlights what is currently known about pulmonary surfactants, protein–lipid complexes with relevant pathophysiological and therapeutic

http://dx.doi.org/10.1016/j.bbamem.2014.03.008
0005-2736/© 2014 Elsevier B.V. All rights reserved.

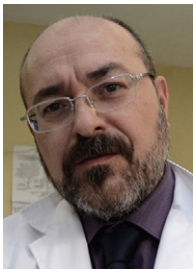
implications. Poveda et al., and Corbalán-García and Gomez-Fernandez each summarize the interactions between lipids and the integral protein channel, KcsA, and the peripheral protein kinase C (PKC), respectively.

The physiological role of membrane lipids in cells as well as their participation in pathological conditions and their therapeutic potential, is the focus of the last section of this special issue. Reuevn and collaborators have reviewed the interactions of the Toll-like receptor transmembrane domains in innate immune responses, and their impact in cancer, Alzheimer's disease and other pathologies. Lladó et al. have reviewed the role of sphingomyelin synthase and related genes in the prognosis and therapy of a brain cancer (glioma). The article by Török et al. highlights the role of plasma membrane lipids as heat stress sensors and the therapeutic applications of this knowledge. Moreover, López et al. review the impact of olive oil intake (Mediterranean diet) on the membrane lipid composition and its relevance for human health. In their second contribution, both Piotto and collaborators, and Nicolson and Ash, review the molecular basis underlying lipid therapies, assessing how they can regulate membrane composition, and thus contribute to normalizing cellular function. Finally, Torres et al. review the effect of hydroxydocosahexaenoic acid on membrane composition in the mouse brain and its possible use and efficacy in the treatment of Alzheimer's disease.

Despite the variety of topics in this Special Issue, one significant feature is clear in all of the articles: they all describe the membrane lipid bilayer as a dynamic and heterogeneous structure with activities that go beyond their simple boundary functions.

References

[1] E. Gorter, F. Grendel, On bimolecular layers of lipoids on the chromocytes of the blood, J. Exp. Med. 41 (1925) 439–443.
[2] J.D. Robertson, The ultrastructure of cell membranes and their derivatives, Biochem. Soc. Symp. 16 (1959) 3–43.
[3] J.F. Danielli, H. Davson, A contribution to the theory of permeability of thin films, J. Cell. Comp. Physiol. 5 (1935) 495–508.
[4] A.A. Benson, On the orientation of lipids in chloroplast and cell membranes, J. Am. Oil Chem. Soc. 43 (1966) 265–270.
[5] D.E. Green, D.W. Allmann, E. Bachmann, H. Baum, K. Kopaczyk, E.F. Korman, S. Lipton, D.H. MacLennan, D.G. McConnell, J.F. Perdue, J.S. Rieske, A. Tzagoloff, Formation of membranes by repeating units, Arch. Biochem. Biophys. 119 (1987) 312–335.
[6] S.J. Singer, G.L. Nicolson, The fluid mosaic model of the structure of cell membranes, Science 175 (1972) 720–731.
[7] G.L. Nicolson, Transmembrane control of the receptors on normal and tumor cells. I. Cytoplasmic influence over cell surface components, Biochim. Biophys. Acta 457 (1976) 57–108.
[8] S. Mabrey, P.L. Mateo, J.M. Strtevant, High-sensitivity scanning calorimetric study of mixture of cholesterol with dimyristoyl- and dipalmitoylphosphatidylcholines, Biochemistry 17 (1978) 2464–2468.
[9] S.E. Lux, Dissecting the red cell membrane skeleton, Nature 281 (1979) 426–429.
[10] F. Giraud, M. Claret, K.R. Bruckdorfer, B. Chailley, Effects of lipid order and cholesterol on the internal and external cation sites of the Na^+–K^+ pump in erythrocytes, Biochim. Biophys. Acta 647 (1981) 249–258.
[11] J.M. González-Ros, M. Llanillo, A. Paraschos, M. Martínez-Carrion, Lipid environment of acetylcholine receptor from *Torpedo californica*, Biochemistry 21 (1982) 3467–3474.
[12] P.L. Yeagle, Lipid regulation of cell membrane structure and function, FASEB J. 3 (1989) 1833–1842.
[13] P.V. Escribá, M. Sastre, J.A. García-Sevilla, Disruption of cellular signaling pathways by daunomycin through destabilization of nonlamellar membrane structures, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 7595–7599.
[14] P.V. Escribá, A. Ozaita, C. Ribas, A. Miralles, E. Fodor, T. Farkas, J.A. García-Sevilla, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 11375–11380.
[15] O. Vögler, J. Casas, D. Capó, T. Nagy, G. Borchert, G. Martorell, P.V. Escribá, The G_i dimer drives the interaction of heterotrimeric G_i proteins with nonlamellar membrane structures, J. Biol. Chem. 279 (2004) 36540–36545.
[16] J. Zimmerberg, K. Gawrich, The physical chemistry of biological membranes, Nat. Chem. Biol. 11 (2006) 564–567.
[17] L.A. Bagatolli, J.H. Ipsen, A.C. Simonsen, O.G. Mouritsen, An outlook on the organization of lipids in membranes: searching for a realistic connection with the organization of biological membranes, Prog. Lipid Res. 49 (2010) 378–389.
[18] G.L. Nicolson, Lipid replacement as an adjunct therapy in chronic fatigue, anti-aging and restoration of mitochondrial function, J. Am. Nutraceut. Assoc. 6 (2003) 22–28.
[19] P.V. Escribá, Membrane-lipid therapy: a new approach in molecular medicine, Trends Mol. Med. 12 (2006) 34–43



Pablo V. Escribá, Ph.D., is the Professor of Cell Biology at the University of the Balearic Islands. He is also the Head of the Molecular Cell Biomedicine Laboratory, the Director of the Graduate Program in Biotechnology and Head of the Oncology Division of the University Institute for Health Science Research of this university. Prof. Escribá is Founder and CSO for Lipopharma Therapeutics. His research is mainly focused on the relationship between membrane lipid structure and cell signaling, its involvement in pathological processes and the rational design of lipids to treat conditions associated with membrane lipid alterations. In this scenario, membrane lipid structure and protein–lipid interactions have been some of the main scientific interests of Prof. Escribá. As a result of his basic science studies, he has designed and patented several molecules and 4 different pharmaceutical companies have started clinical trials in humans with molecules designed by Prof. Escribá. These molecules regulate the membrane lipid structure and have shown therapeutic potential for the treatment of cancer, metabolic diseases and Alzheimer disease. He is a referee for National and Foreign Research Agencies and scientific journals, and has published about one hundred works and six patents, most of them focused on "membrane lipid therapy".

Professor Garth L. Nicolson is the President, Chief Scientific Officer and Research Professor at the Institute for Molecular Medicine in Huntington Beach, California. He is also a Conjoint Professor at the University of Newcastle (Australia). He was formally the David Bruton Jr. Chair in Cancer Research and Professor and Chairman of the Department of Tumor Biology at the University of Texas M. D. Anderson Cancer Center in Houston, and he was Professor of Internal Medicine and Professor of Pathology and Laboratory Medicine at the University of Texas Medical School at Houston. He was also Professor of Comparative Pathology at Texas A & M University. Professor Nicolson has published over 600 medical and scientific papers, including editing 19 books, and he has served on the Editorial Boards of 30 medical and scientific journals and was a Senior Editor of four of these. Professor Nicolson has won many awards, such as the Burroughs Wellcome Medal of the Royal Society of Medicine (United Kingdom), Stephen Paget Award of the Metastasis Research Society, the U. S. National Cancer Institute Outstanding Investigator Award, and the Innovative Medicine Award of Canada. He is also a Colonel (Honorary) of the U. S. Army Special Forces and a U. S. Navy SEAL (Honorary) for his work on the Armed Forces and veterans' illnesses.

Pablo V. Escribá*
Department of Biology, University of the Balearic Islands, Spain
*Corresponding author at: Dept. of Biology, University of the Balearic Islands, Ctra. de Valldemossa km 7, E-07122 Palma de Mallorca, Spain
E-mail address: pablo.escriba@uib.es.

Garth L. Nicolson
Institute for Molecular Medicine, Huntington Beach, CA, USA