Progress in Lipid Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Membrane lipid therapy: Modulation of the cell membrane composition and structure as a molecular base for drug discovery and new disease treatment

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ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 10 April 2015
Accepted 29 April 2015
Available online xxxx

Dedicated to the memory of our late colleague and friend, Professor John E. Halver.

ABSTRACT

Nowadays we understand cell membranes not as a simple double lipid layer but as a collection of complex and dynamic protein–lipid structures and microdomains that serve as functional platforms for interacting signaling lipids and proteins. Membrane lipids and lipid structures participate directly as messengers or regulators of signal transduction. In addition, protein–lipid interactions participate in the localization of signaling protein partners to specific membrane microdomains. Thus, lipid alterations change cell signaling that are associated with a variety of diseases including cancer, obesity, neurodegenerative disorders, cardiovascular pathologies, etc. This article reviews the newly emerging field of membrane lipid therapy which involves the pharmacological regulation of membrane lipid composition and structure for the treatment of diseases. Membrane lipid therapy proposes the use of new molecules specifically designed to modify membrane lipid structures and microdomains as pharmaceutical disease-modifying agents by reversing the malfunction or altering the expression of disease-specific protein or lipid signal cascades. Here, we provide an in-depth analysis of this emerging field, especially its molecular bases and its relevance to the development of innovative therapeutic approaches.

Abbreviations: AA, arachidonic acid; Aβ, fibrillar β-amyloid; ACC, acetyl-CoA carboxylase; Akt, protein kinase B; APP, amyloid precursor protein; ASAH2, neutral ceramidase; BA, benzyl alcohol; BBB, blood–brain-barrier; BMI, body mass index; BPM, bis(monoacylglycero)phosphate; CALM, clathrin assembly lymphoid myeloid domains; CAMKII, calcium/calmodulin-dependent protein kinase II; Cav1, caveolin 1; Cer, ceramide; Chol, cholesterol; CNS, central nervous system; DAG, diacylglycerol; DHA, docosahexaenoic acid; EGFR, endothelial growth factor receptor; ENTH, epsin N-terminal homology domains; EPA, eicosapentaenoic acid; FA, fatty acid; FASN, fatty acid synthase gene; FERM, 4.1 protein-ezrin-radixin-moesin; GEM, glycolipid-enriched membrane microdomain; GLRX, glutaredoxin; GM, monosialodihexosylganglioside; GPCRs, G protein coupled receptors; GSLs, glycosphingolipids; HA, hydroxamic acid; HSF1, heat shock factor 1; Hsp, heat shock proteins; Hsp27, heat shock protein 27; Hsp70, heat shock protein 70; HSR, heat shock response; INSIG1, insulin-induced gene 1; IR, insulin receptor; Ld, liquid disordered microdomains; Lo, liquid ordered microdomains; LDL, low density lipoprotein; LXR, liver X receptor; MAPK, mitogen activated protein kinase; MLT, membrane lipid therapy; MUFA, monounsaturated fatty acids; NMDA, N-methyl-D-aspartate; OLR1, oxidized low-density protein receptor 1; PC, phosphatidylcholine; PDGFR, platelet derived growth factor receptor; PDZ domain, PSD95-Dlg1-zo-1 domains; PE, phosphatidylethanolamine; PH domain, pleckstrin homology domain; PHYH, phytanoyl CoA dioxygenase; PIP2, phosphatidylinositol 4,5-bisphosphate; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLA2, phospholipase A2; PLC, phospholipase C; PPARs, peroxisome proliferator-activated receptors; PTB domain, phosphotyrosine-binding domain; PUFA, polyunsaturated fatty acid; PYVE domain, Fab-1, YGL023, Vps27, and EEA1 domain; RAR, retinoic acid receptor alpha; REMBRANDT, repository for molecular brain neoplasia data; RXR, retinoid X receptor; S1P, sphingosine-1-phosphate; SCI, spinal cord injury; SGMS1/2, sphingomyelin synthase; SM, sphingomyelin; SMPD2/3, SM phosphodiesterase 2/3 (neutral sphingomyelinases); SNAP23, synaptosomal-associated protein 23; SPC, sphingosylphosphorylcholine; SPHK1/2, sphingosine kinase; SPTLC3, palmitoyltransferase; SREBP1, sterol regulatory element-binding protein 1; TAG, triacylglycerol; TCGA, cancer genome atlas; TNF-α, tumor necrosis factor alpha; UGCG, ceramide glucolsyltransferase; VLDL, very low density lipoprotein.

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http://dx.doi.org/10.1016/j.plipres.2015.04.003
0163-7827/

Contents

1. Introduction

Since the first general structure of cellular membranes was published in the 1970s by Singer and Nicolson [1] numerous studies have expanded upon this to further define its complex structure. In a cell membrane bilayer, hundreds to thousands of different lipid species form a heterogeneous cell boundary with multiple structural and functional properties [2]. The same membrane sequestration strategy that separates the interior of cells from the rest of world is also used for separating the cellular interior into a collection of membrane-bound organelles. The lipid classes that form the different types of cell membranes (Fig. 1) are usually not homogeneously distributed but can form microdomains that act as complex signaling platforms (together with proteins) due to their membrane lipid (structure) preferences. For example, interaction of receptor tyrosine kinases (e.g., EGFR) with Ras, and of Ras with Raf, to propagate proliferation signals into the cell benefits from their common preference for certain membrane microdomains to establish physical productive interactions [3]. Similarly, G protein-coupled receptors (GPCRs) and G proteins exhibit similar membrane lipid environment preferences [2,4,5].

Membrane functions are altered in a wide range of human diseases and this has led to the concept that components of the plasma membrane, for example, specific lipids, enzymes or transcription factors can be targeted to alter its composition and structure [6–8]. This, in turn, would affect the localization and activity of key proteins, or key protein–protein interactions in specific membrane microdomains, and thereby affect signaling cascades. This approach is termed membrane lipid therapy (MLT). Indeed, several studies have now demonstrated the potential of MLT and, although the first clinical trials of rationally designed lipids to regulate the membrane composition and structure to treat cancer and diabetes only began recently (e.g., ClinicalTrials.gov Identifier NCT01792310), other trials using natural lipids were already ongoing (e.g., docosahexaenoic acid (DHA) for Alzheimer's disease: ClinicalTrials.gov Identifier NCT00440050). In this article, the rationale behind targeting the plasma membrane and the different approaches that can be used to modulate its lipid composition, structure and function is provided. Later, we discuss the current state of the art in various therapeutic indications.

2. Molecular bases underlying MLT

A great many cellular functions occur in or around membranes [2], which suggests that changes in the membrane composition and structure could be relevant in the proper functioning of the cells. In the plasma membrane, hundreds of different lipid species can be found. Some of them have a negative charge, which can promote interactions with positively charged amino acids in proteins [4,7]. Other lipids have a small polar head (e.g., phosphatidylethanolamine), allowing docking of bulky protein lipid anchors (e.g., isoprenyl moieties present in Ras: [9]). Other membrane lipids have a bigger polar head and form tightly packed areas where only certain fatty acids (e.g., myristic or palmitic acid) can intercalate to aid proteins (e.g., Gα protein) bind to membrane regions where these lipids are abundant. Therefore, the membrane lipid composition can have a profound role in cell signaling. Changes in the type and abundance of lipids in membranes induce alterations in the propagation of cell messages that can be associated with pathological states or with its therapy. In the following paragraphs we will describe important structural features of membranes and proteins that participate in protein–lipid interactions and can be regulated by MLT drugs.

Thus, it has been seen that a high consumption of saturated or trans-unsaturated fatty acids induce increases in the proportion of

Please cite this article in press as: Escribá PV et al. Membrane lipid therapy: Modulation of the cell membrane composition and structure as a molecular base for drug discovery and new disease treatment. Prog Lipid Res (2015), http://dx.doi.org/10.1016/j.plipres.2015.04.003