Biochimica et Biophysica Acta 1791 (2009) 636–645

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Intracellular sterol dynamics

Bruno Mesmin, Frederick R. Maxfield *

Department of Biochemistry, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA

ARTICLE INFO

Article history:
Received 23 December 2008
Received in revised form 27 February 2009
Accepted 3 March 2009
Available online 12 March 2009

Keywords:
Cholesterol
Lipid
Membrane
Bilayer
Transport

ABSTRACT

We review the cellular mechanisms implicated in cholesterol trafficking and distribution. Recent studies have provided new information about the distribution of sterols within cells, including analysis of its transbilayer distribution. The cholesterol interaction with other lipids and its engagement in various trafficking processes will determine its proper level in a specific membrane; making the cholesterol distribution uneven among the various intracellular organelles. The cholesterol content is important since cholesterol plays an essential role in membranes by controlling their physicochemical properties as well as key cellular events such as signal transduction and protein trafficking. Cholesterol movement between cellular organelles is highly dynamic, and can be achieved by vesicular and non-vesicular processes. Various studies have analyzed the proteins that play a significant role in these processes, giving us new information about the relative importance of these two trafficking pathways in cholesterol transport. Although still poorly characterized in many trafficking routes, several potential sterol transport proteins have been described in detail; as a result, molecular mechanisms for sterol transport among membranes start to be appreciated.

1. Introduction

Understanding intracellular sterol dynamics is very important because the proper abundance of sterol in the plasma membrane (PM) and organelle membranes is critical for many cellular functions. Sterol is carried between membrane organelles as a component of lipid bilayers in transport vesicles, and it is also moved between membranes by non-vesicular processes using poorly characterized mechanisms involving carrier proteins. The overall rates of sterol transport among organelles can be very rapid (i.e., re-equilibration between two organelles within a few minutes).

Among the major lipids found in membranes of eukaryotic cells, sterols have the most atypical chemistry, containing a single hydroxyl as the only polar component, a nearly planar assembly of four rings, and a short alkyl chain [1]. This structure contrasts with most glycerophospholipids and sphingolipids, with their large polar headgroups and long hydrocarbon tails. These molecular characteristics give sterols an influential role in the physicochemical properties of the membrane as well as the ability to move rapidly between the two membrane leaflets (flip-flop). Compared to other lipids, sterols have a lower free energy barrier to escape from the lipid bilayer [2]. Sterols, like other lipids, can be shuttled by soluble carrier proteins from one membrane to another, and this can allow rapid transport among the membranes in a cell. These transport properties may allow sterols to approach a state of chemical equilibrium among some cellular membranes (i.e., the *chemical activity* of cholesterol, the thermodynamic measure of availability for a chemical or physical transition, may be nearly equal among these cellular membranes). Nevertheless, the *concentration* of cholesterol could still vary greatly among these membranes as a consequence of the relative stabilization of sterol in the various membranes by other constituents. That is, the *chemical activity coefficient* of cholesterol may be lowered by favorable interactions. ($a = \gamma c$; where a is chemical activity, c is concentration, and γ is the chemical activity coefficient. At equilibrium, the chemical activity of cholesterol in various membranes would be equal, but if the membranes had different activity coefficients, the concentrations could be unequal).

In studies of model membrane systems, the biophysical basis for the relative stabilization of sterols in various membranes, based on sterol–lipid interactions, has been described using various models, including the "umbrella model" [3] that underlines the necessity for a sterol molecule to be protected from the water by other lipids for its stabilization, and the "condensed complex model" [4], which describes the formation of stoichiometric complexes of low free energy between cholesterol and lipids. Recent studies in cells have provided new information about the distribution of sterols within

Abbreviations: PM, plasma membrane; ER, endoplasmic reticulum; ERC, endosomal recycling compartment; LE, late endosome; LY, lysosome; LSO, LE/LY-like storage organelle; PC, phosphatidylcholine; SM, sphingomyelin; PS, phosphatidylserine; PE, phosphatidylethanolamine; DO, dioleoyl; DP, dipalmitoyl; BMP, bis-(monoacylglycerol)-phosphate; DHE, dehydroergosterol; CTL, cholestatrienol; TNBS, trinitrobenzenesulfonate; CHO, Chinese hamster ovary; ATP, adenosine triphosphate; ABC, ATP-binding cassette; NPC, Niemann-Pick type C; SSD, sterol-sensing domain; LTP, lipid transfer protein; OSBP, oxysterol-binding protein; StAR, steroidogenic acute regulatory protein; ACAT, acyl-CoA cholesterol acyl transferase; LAL, lysosomal acid lipase; LDL, low-density lipoprotein; HDL, high-density lipoprotein

* Corresponding author. Tel.: +1 212 746 6405; fax: +1 212 746 8875.
E-mail address: frmaxfie@med.cornell.edu (F.R. Maxfield).

1388-1981/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbalip.2009.03.002

cells, including analysis of its transbilayer distribution. At the same time, genetic and biochemical studies have analyzed the proteins that play an important role in sterol transport, and structural studies of sterol transport proteins are beginning to demonstrate the molecular mechanisms for sterol transport among membranes.

In this review, we will first focus on recent work on cholesterol–lipids interactions and try to reconcile these studies with latest findings in cellular sterol distribution. New findings on sterol transbilayer distribution will be discussed as well. Then, we will focus on the sterol transport between the different organelle membranes.

2. Cholesterol–phospholipid interactions

2.1. Biophysical concepts and sterol chemical activity

The umbrella model [3] and the condensed complex model [4] take different approaches to analyze sterol stability in various lipid membrane environments based on interactions with neighboring phospholipids. The umbrella model is based on the amphipathic structural mismatch of the cholesterol molecule with other lipids in the bilayer: its small hydroxyl head facing the aqueous milieu only partially protects the hydrophobic ring system from water. Since this water exposure is very unfavorable, the sterol associates with neighboring phospholipids with larger polar headgroups in order to shield its hydrophobic rings from water (Fig. 1). As a result, phospholipids like phosphatidylcholine (PC) or sphingomyelin (SM) bearing relatively large headgroups (~70 Å^3) [5] would be preferred partners for cholesterol as compared to phosphatidylethanolamine (PE), which possesses a smaller polar head (~40 Å^3). Indeed, a PC "umbrella" can shield two cholesterol molecules whereas only one cholesterol molecule can take cover under a PE headgroup [3]. In addition to the size of the headgroup, the level of acyl chain unsaturation is important for understanding sterol stabilization within the framework of the umbrella model because of effects on lipid geometry within the bilayer [6]. As depicted in Fig. 1, greater unsaturation leads to a conical shape because of the relative large cross section of the acyl chains as compared to the headgroup, whereas saturated lipids tend to be more cylindrical. The headgroup/body size ratio of conical lipids, like dioleoyl-PC (DOPC), is less well suited to shield neighboring sterol molecules than dipalmitoyl-PC (DPPC), with its two saturated acyl chains [6].

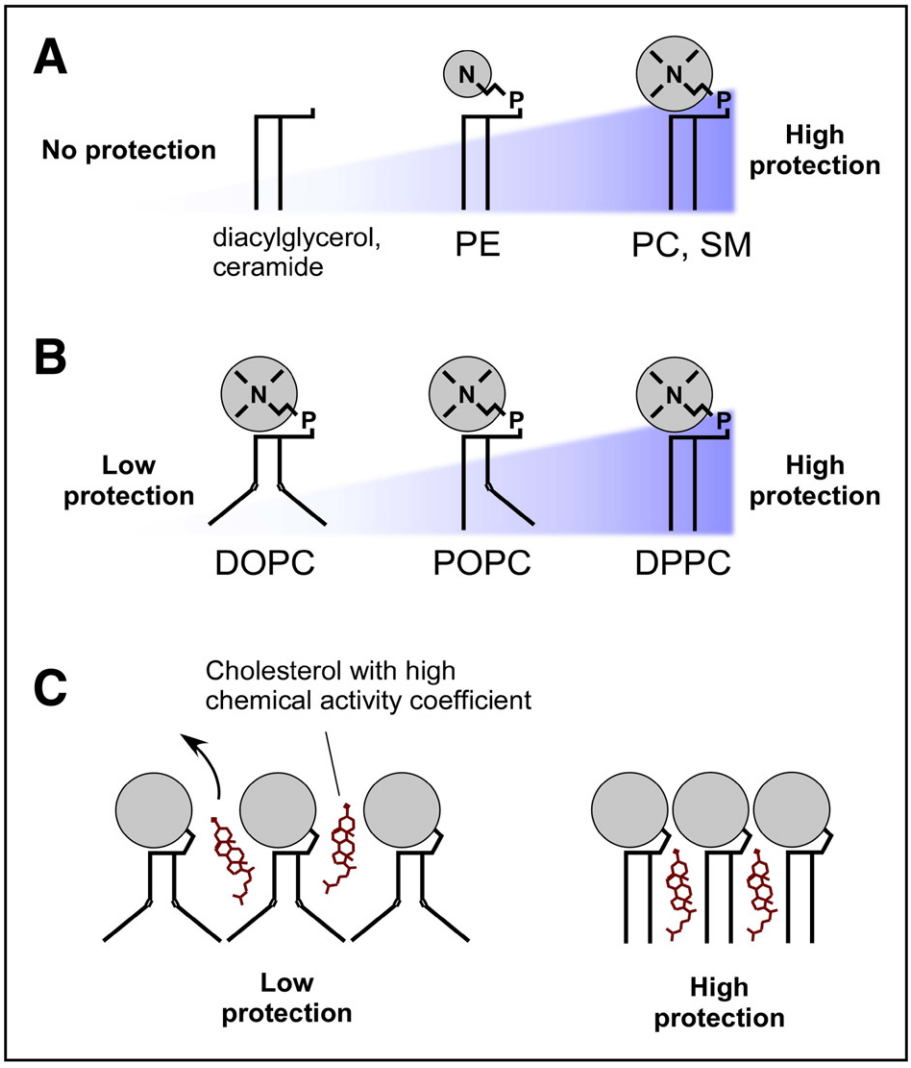

Fig. 1. Structural interactions between cholesterol and other lipids. The sterol stability in a membrane depends on its interaction with neighboring lipids. (A) Lipids bearing large polar head groups are preferred partners for cholesterol because they provide better protection from water. (B) The level of acyl chain saturation also influences the sterol stability because it is directly related to the lipid shape. Lipids with unsaturated acyl chains containing one double bond are more bulky than lipids with saturated chains; these unsaturated lipids are less suited to afford protection from water to the neighboring cholesterol. C. Poorly protected sterols (e.g., in a DOPC-rich bilayer) have a high chemical activity coefficient; they can leave the membrane readily. In contrast, well protected sterols form with their associated lipids a structure of low chemical activity coefficient. DOPC, dioleoyl-phosphatidylcholine (PC); POPC, palmitoyl-oleoyl-PC; DPPC, dipalmitoyl-PC.