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Review

Checks and balances in membrane phospholipid class and acyl chain homeostasis, the yeast perspective ☆

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ABSTRACT

Glycerophospholipids are the most abundant membrane lipid constituents in most eukaryotic cells. As a consequence, phospholipid class and acyl chain homeostasis are crucial for maintaining optimal physical properties of membranes that in turn are crucial for membrane function. The topic of this review is our current understanding of membrane phospholipid homeostasis in the reference eukaryote *Saccharomyces cerevisiae*. After introducing the physical parameters of the membrane that are kept in optimal range, the properties of the major membrane phospholipids and their contributions to membrane structure and dynamics are summarized. Phospholipid metabolism and known mechanisms of regulation are discussed, including potential sensors for monitoring membrane physical properties. Special attention is paid to processes that maintain the phospholipid class specific molecular species profiles, and to the interplay between phospholipid class and acyl chain composition when yeast membrane lipid homeostasis is challenged. Based on the reviewed studies, molecular species selectivity of the lipid metabolic enzymes, and mass action in acyl-CoA metabolism are put forward as important intrinsic contributors to membrane lipid homeostasis.

Contents

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1. Introduction

Cells and intracellular compartments are separated from their environment by a barrier with a thickness in the range of 5–9 nm. These barriers, commonly known as membranes, are composed of a matrix of lipid molecules arranged in two layers or leaflets. The hydrophobic part of the lipids in each layer is directed inward, while the hydrophilic headgroups are exposed to the aqueous environment. The hydrophobic core renders membranes virtually impermeable for polar compounds. Each cellular membrane harbors its own unique set of proteins that is required for the functions of the enclosed compartment. The proteins embedded in and associated with the lipid bilayer perform a plethora of functions including the transport of polar compounds across the membrane, energy transduction, and the transfer of information in response to external stimuli.

Biological membranes not only vary in the proteins associated with them, but also in their lipid composition. Thousands of different lipid molecules have been identified in the lipidome of cellular membranes, each with its own unique properties, indicating that lipids do not only serve as passive membrane building blocks. They for instance create the appropriate environment for optimal catalytic activity and/or stability of membrane proteins. Therefore, knowledge of the mechanisms maintaining membrane lipid homeostasis is of paramount importance for understanding membrane functions and processes.

Membrane lipids can be divided in different families based on their molecular structure, with glycerophospholipids, glycoglycerolipids (in chloroplasts), sterols and sphingolipids being most abundant in eukaryotes. This review focuses on the regulation of membrane lipid homeostasis in the reference eukaryote *Saccharomyces cerevisiae*, a unicellular eukaryote commonly known as baker's yeast with longstanding and widely appreciated applications in bakeries and breweries. *S. cerevisiae*'s short cell cycle and the wide range of available molecular biology tools and genetic screens make it very suitable for biochemical and cell biological research. It is probably the best understood eukaryotic organism and an ideal model for higher eukaryotes because of the many homologies at the gene and protein levels.

In yeast, as in most other eukaryotes, the glycerophospholipids, from now on referred to as phospholipids, are the most abundant membrane lipids constituting some 70% of the membranes' lipid matrix [1]. Ergosterol (the yeast sterol) and the sphingolipids inositolphosphorylceramide (IPC), mannosyl-inositolphosphorylceramide (MIPC) and mannosyl-diinositolphosphorylceramide ($M(IP)_2C$) account for the remainder and are particularly abundant in the plasma membrane [2]. Phospholipid composition and synthesis are similar in yeast and mammalian cells. The phospholipids are subdivided in classes according to the nature of their polar headgroup with each class consisting of numerous molecular species, i.e. phospholipid molecules varying in the length and number of double bonds in their fatty acyl chains. Baker's yeast has a simple fatty acid profile compared to higher eukaryotes and lacks alkyl glycerolipids and sphingomyelin, facilitating membrane lipid analysis. Moreover, studies on mutant strains have shown that yeast can tolerate huge variations in membrane lipid composition rendering it the eukaryote of choice for investigating mechanisms and underlying principles that safeguard membrane integrity and function.

In the following, we will seek a better understanding of the mechanisms shaping bulk membrane phospholipid and acyl chain composition in yeast. First the physical properties of membranes determined by lipid composition will be discussed, followed by a concise overview of the properties and functions of the individual phospholipid classes. The biosynthesis of the phospholipids and its regulation will be briefly summarized. The processes and enzymes governing acyl chain homeostasis will be reviewed, followed by a short overview of (putative) membrane sensors. Next, the processes that determine phospholipid class specific acyl chain composition will be reviewed. Against this background, we will describe examples of the interplay between phospholipid class and acyl chain composition, including implications for the regulation of membrane lipid homeostasis.

2. Phospholipid composition determines the physical properties of the membrane

The lipid matrix of biological membranes is a complex assembly of different lipid molecules, tailored to the function of the particular membrane. The lipids constituting the bulk of the membrane lipid matrix determine generic physical properties of the membrane including membrane surface charge, membrane thickness, membrane fluidity, and membrane intrinsic curvature. For proper membrane structure and dynamics it is essential that these parameters are maintained in the appropriate range, also under varying environmental conditions. In addition, comparatively small quantities of lipid molecules are present or can be generated in the membrane, which serve functions in molecular recognition events

Table 1
Gel to liquid crystalline (T_m) phase transition temperatures (°C) of PC and PE and liquid crystalline to hexagonal H_{II} (T_H) phase transition temperatures of PE for a set of fully hydrated PC and PE molecular species relevant in yeast.[a]

*sn*1/*sn*2 acyl chains	T_m PC	T_m PE	T_H PE
18:0/18:0	54.5 ± 1.5	73.7 ± 1.4	101.8 ± 4.3
16:0/16:0	41.3 ± 1.8	62.3 ± 5.0	120.6 ± 3.6
16:1/16:1	−35.5[b]	−33.5	43.4 ± 0.2
16:0/18:1	−2.5 ± 2.4	24.4 ± 1.6	70.8 ± 2.5
18:1/18:1	−18.3 ± 3.6	−7.3 ± 3.8	8.5 ± 1.9

[a]Data for PC taken from [262] and [b][263]; data for PE taken from [264].