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Review article

Phosphatidylglycerol-derived phospholipids have a universal, domain-crossing role in stress responses

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ABSTRACT

Phosphatidylglycerol and phospholipids derived from it are widely distributed throughout the three domains of life. Cardiolipin is the best characterized of these phospholipids, and plays a key role in the response to environmental variations. Phosphatidylglycerol-derived phospholipids confer cell membranes with a wide range of responses, including changes in surface charge, fluidity, flexibility, morphology, biosynthesis and remodeling, that adapt the cell to these situations. Furthermore, the synthesis and remodeling of these phospholipids is finely regulated, highlighting the importance of these lipids in cell homeostasis and responses during stressful situations. In this article, we review the most important roles of these anionic phospholipids across domains, focusing on the biophysical basis by which these phospholipids are used in stress responses.

Contents

1. Introduction

Membranes are the key cellular elements to isolate metabolic processes from the environment. As a result, specific adaptations evolved to provide cell and organelle membranes with the versatility to respond and maintain cell integrity. One such adaptation is the maintenance of a balance between zwitterionic and anionic phospholipids [1,2]; the proportion between these classes of phospholipids depends on the regulation of their synthesis pathways [3]. In general, anionic phospholipids such as phosphatidylserine (PS), the phosphatidylinositol (PI) family and the phosphatidylglycerol (PG) family are synthesized by the CDP-DAG

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dependent pathway, whilst zwitterionic phospholipids are synthesized by the Kennedy pathway and in some cases by modifying PS [4–6]. Representative examples of zwitterionic lipids are phosphatidylethanolamine (PE) and phosphatidylcholine (PC).

The anionic phospholipid PS is not widely distributed phylogenetically despite the fact that it is effectively synthesized. It does not accumulate because it is rapidly consumed to produce PE [7,8]. As a result, bacteria and archaea have an insignificant content in their membranes. On the other hand, phosphatidylglycerol-derived phospholipids are widely distributed across domains (see the structures of some of these phospholipids in Fig. 1). The main representatives of this family are PG and cardiolipin (CL). PG is also the precursor of domain-specific anionic phospholipids such as phosphatidylglycerol phosphate (PGP), phosphatidylglycerol phosphate methyl ester (PGPM) and phosphatidylglycerol sulfate (PGS) for archaea [9] and carbohydrate- and amino acid derivatives of PG in bacteria [10]. Despite the variety of members in this family, the most prominent member is CL.

The presence of CL in the three domains suggests a convergent evolution of its synthesis pathways. However, the eukarya domain domain uses a different group of enzymes, and a detailed analysis of this pathway showed that it has a dual origin in which the archaeal host and the bacterial endosymbiont equally contributed toward providing enzymes for the eukaryotic pathway [11]. From this perspective, it is tempting to say that CL functions are related to metabolic pathways. Indeed, CL is firmly attached to membrane proteins such as cytochrome *c* oxidase, from archaea and eukaryotes, where it exerts regulatory properties [12,13]. Other functions seem not to be widely conserved since archaea and bacteria upregulate the enzyme synthesizing CL only under specific situations, such as in the stationary phase [14]. The reason for this divergent behavior could reside in the intrinsic order of the enzymes in the pathway. In eukaryotes, CL is continuously synthesized and remodeled thanks to the presence of a cardiolipin synthase dependent on CDP-DAG, a high energy compound [15,16]. This subtle difference exhausts the pool of PG and maintains a high basal CL level. On the other hand, in bacteria and archaea, phospholipase D cardiolipin synthase (Fig. 2) is highly promiscuous and is able to replenish the pool of PG, the main anionic phospholipid in these membranes [17].

Although both are anionic, CL and PG present very different biophysical properties. PG contains one negative charge at physiological pH while CL presents one or two charges [18]. The presence of two ionizable groups allows proton stabilization in a resonance-like process [19]. Moreover, the acyl chain content defines the morphology of both lipids. PG is a mostly tubular, bilayer forming, lipid and this conformation is mostly independent of the nature of the acyl chains (Fig. 1). On the other hand, the four acyl chains in CL permit non-lamellar conformations (less hydrated and packed than lamellar phases) such as hexagonal as well as lamellar assemblies [20] (for an excellent review on lipid phase transition and its biological implication see [21]). This pleiomorphic behavior is promoted by the small size of the CL head group (a glycerol linking two phosphate groups) relative to the acyl chains (see Fig. 1). These conformational properties could be important for mitochondrial morphology and dynamics.

The negative charge in CL is an important player in the maintenance of the membrane surface charge, which will ultimately affect the permeability barrier of the membrane [22]. It also plays a pivotal role in osmotic stress by shielding positive charges near the interface and stabilizing non-ionic osmolites in the water–lipid interface [23]. Indeed, the stabilization of osmolites (ionic or not) at the interface produces a vitrification effect on the membrane, retaining water molecules indispensable for the function of membrane proteins [24].

As mentioned above, all PG family members have a crucial role in cell physiology, mainly involving the stress response. Specific cases will be discussed in the next sections.

2. CL in the eukarya domain

2.1. CL biosynthesis and remodeling

Unlike bacteria, eukaryotes present two sequential groups of reactions that produce mature CL (Fig. 2). The first group includes the biosynthetic enzymes PGP synthase (Pgs), PGP phosphatase and cardiolipin synthase (Cls) [25]. The second block includes the enzymes responsible for maturing CL, an A2 phospholipase (Cld1p in yeast) and a transacylase named tafazzin [26]. None of these enzymes in CL biosynthesis present orthologues in bacteria (Fig. 2), which could suggest a possible convergent evolutionary mechanism in both domains. However, another mechanism has been proposed for the origin of the eukaryotic pathway, a scenario in which both archaeal and bacterial pathways fused during endosymbiosis which gave rise to mitochondria. Later, speciation, diversification and secondary (and tertiary) endosymbiotic processes reshaped this metabolic pathway [11]. Remodeling seems to be a trait of eukaryotes, since neither tafazzin nor CL-specific phospholipase A2 were ever found in bacteria or archaea [27].

CL deficiency in eukaryotes produces pleiotropic phenotypes, indicating that CL is important for overall mitochondrial function [28]. A common feature of cells lacking CL is the presence “giant” mitochondria [29]. CL confers the inner membrane with specific elastic and viscous properties, allowing for reversible low amplitude swelling and contraction cycles [30]. This may be especially important under non-permissive conditions, such as inadequate temperature, salinity and osmolarity. Indeed, a yeast strain devoid of Cls accumulates PG under permissive situations (28 °C), stabilizing mitochondrial membranes. Under non-permissive conditions (37 °C), homeoviscous adaptations, or the ability of the cell to maintain membrane viscosity, are not attained and the cells lose their mtDNA because of a deficiency in mitochondrial segregation [31]. Indeed, CL binds strongly to mtDNA and guides its segregation under stressful conditions, ensuring the maintenance of mitochondrial function [31].

In eukaryotes, CL is further processed to produce mature CL; saturated CL produced in the first steps of the pathway is actively unsaturated, a process called remodeling. However, CL remodeling appears not to be essential for basic mitochondrial homeostasis, since the presence of saturated CL substitutes for unsaturated CL [32,33]. Barth syndrome, a severe genetic disease produced by mutations in the tafazzin gene, is characterized by the decreased or null reacylation of monolysoCL (MLCL), the product of the phospholipase A2 [34]. Apparently it is not the lack of remodeling, but the ratio of MLCL/CL, that is responsible for characteristics this disease [35]. Several new roles for tafazzin have been described and could be related to the phenotypes observed in Barth syndrome. Swollen mitochondria, altered cristae morphology and impaired mitophagy are all related to the lack of unsaturated CL and increased MLCL/CL ratios [36–38]. Both the anionic headgroup and the acyl chain composition act cooperatively to confer CL with its biological activity. In this regard, membrane models with MLCL as the only anionic phospholipid are not responsive to sodium ions or pH at the membrane interface, a finding which has profound physiological significance [20,40]. Indeed, liposomes mimicking mitochondrial membranes respond to local pH gradients, forming tubular structures similar to cristae in the mitochondrial inner membrane [41,42]. Protons screen the CL anion and favor a transition from lamellar to hexagonal phases. MLCL charges screened with