Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Bacterial lipid diversity☆

Isabel M. López-Lara, Otto Geiger *

Centro de Ciencias Genómicas, Universidad Nacional Autónoma de México, Av. Universidad s/n, Apdo, Postal 565-A, Cuernavaca, Morelos CP62210, Mexico

ARTICLE INFO

Article history:
Received 10 September 2016
Received in revised form 10 October 2016
Accepted 11 October 2016
Available online xxxx

Keywords:
Membrane lipid biosynthesis
Phospholipid
Lipid remodeling
Lipid cycle
Lipid turn-over

ABSTRACT

The glycerophospholipids phosphatidylethanolamine, phosphatidylglycerol (PG), and cardiolipin (CL) are major structural components of bacterial membranes. In some bacteria, phosphatidylcholine or phosphatidylinositol and its derivatives form part of the membrane. PG or CL can be modified with the amino acid residues lysine, alanine, or arginine. Diacylglycerol is the lipid anchor from which syntheses of phosphorus-free glycerolipids, such as glycolipids, sulfolipids, or homoserine-derived lipids initiate. Many membrane lipids are subject to turnover and some of them are recycled. Other lipids associated with the membrane include isoprenoids and their derivatives such as hopanoids. Ornithine-containing lipids are widespread in Bacteria but absent in Archaea and Eukarya. Some lipids are probably associated exclusively with the outer membrane of many bacteria, i.e. lipopolysaccharides, sphingolipids, or sulfonolipids. For certain specialized membrane functions, specific lipid structures might be required. Upon cyst formation in *Azotobacter vinelandii*, phenolic lipids are accumulated in the membrane. Anammox bacteria contain ladderane lipids in the membrane surrounding the anammoxosome organelle, presumably to impede the passage of highly toxic compounds generated during the anammox reaction. Considering that present knowledge on bacterial lipids was obtained from only a few bacterial species, we are probably only starting to unravel the full scale of lipid diversity in bacteria. This article is part of a Special Issue entitled: Bacterial Lipids edited by Russell E. Bishop.

1. Introduction

Departing from the classical definition that any compound not soluble in water is a lipid, it comes as no surprise that lipids would occupy a large chemical space with numerous chemically diverse structures. However, the major and best-known lipid classes are probably storage lipids in the form of triglycerides and membrane-forming lipids such as glycerophospholipids [1] and at first sight, their structural variations seem to be rather limited. As only few bacteria can form triglycerides, their function of storage lipids is essentially limited to eukaryotes. In contrast, due to their amphiphilic nature and their near cylindrical shape, membrane glycerophospholipids are main components of cellular membranes in the three domains of life, Eukarya, Archaea, and Bacteria. In the glycerophospholipids of Bacteria and Eukarya, fatty acyl side chains are linked via ester bonds to a *sn*-glycerol-3-phosphate backbone. In contrast, isoprenoid hydrocarbon side chains are linked via ether bonds to *sn*-glycerol-1-phosphate in glycerol-based membrane lipids of Archaea [2]. These three distinctive features (1) fatty acyl versus isoprenoid, (2) ester versus ether, and (3) *sn*-glycerol-3-phosphate versus *sn*-glycerol-1-phosphate constitute what is known as the "lipid divide" [3] and they were major arguments to support the idea that Bacteria and Archaea should be considered as distinct domains of life in addition to the Eukarya domain.

In this review we will try to give an overview on lipids that form membranes or integrate into membranes within the Bacteria domain as well as on the biosynthetic pathways employed for their formation and turn-over.

2. Synthesis of phosphatidic acid and CDP-diacylglycerol (CDP-DAG)

One of the main hallmarks for the so-called lipid divide between Archaea and Bacteria is the stereochemistry of the glycerol-phosphate backbone in membrane lipids [3], which is fixed in the initial step of glycerolipid biosynthesis. The glycolysis intermediate dihydroxyacetone phosphate is converted to *sn*-glycerol-1-phosphate by glycerol-1-phosphate dehydrogenase (encoded by *egsA*) in Archaea [4] or to *sn*-

Abbreviations: AP, alkylpyrone; AR, alkylresorcinol; CL, cardiolipin; CPT, CDP-choline, 1,2-diacylglycerol cholinephosphotransferase; DAG, diacylglycerol; DGTS, diacylglyceryl-*N*,*N*,*N*-trimethylhomoserine; DGHS, diacylglyceryl-lhomoserine; DMPE, dimethylphosphatidylethanolamine; G3P, *sn*-glycerol-3-phosphate; GL, glycosyl diacylglycerol; GPC, glycerol-phosphocholine; LL, lysine lipid; LOL, lyso-ornithine lipid; MAG, monoacylglycerol; MMPE, monomethylphosphatidylethanolamine; OL, ornithine lipid; PA, phosphatidic acid; PC, phosphatidylcholine; Pcs, phosphatidylcholine synthase; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PGP, phosphatidylglycerol phosphate; PI, phosphatidylinositol; PIP, phosphatidylinositol phosphate; Pmt, phospholipid *N*-methyltransferase; PS, phosphatidylserine; SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine; SQDG, sulfoquinovosyl diacylglycerol.

☆ This article is part of a Special Issue entitled: Bacterial Lipids edited by Russell E. Bishop.

* Corresponding author.
E-mail address: otto@ccg.unam.mx (O. Geiger).

http://dx.doi.org/10.1016/j.bbalip.2016.10.007
1388-1981/

glycerol-3-phosphate (G3P) by the "biosynthetic" glycerol-3-phosphate dehydrogenase (encoded by *gpsA*) in Bacteria [5](Fig. 1). Bacteria can obtain G3P also directly from the environment employing the GlpT organophosphate: phosphate antiporter or through the uptake (by the aquaglyceroporin GlpF) and phosphorylation (by glycerol kinase GlpK) of glycerol [6].

The first acylation of G3P occurs at the *sn*-1 position and can be performed by members belonging to two distinct protein families PlsB or PlsY. The PlsB acyltransferase was initially described in *E. coli* [7,8] and uses primarily acyl-acyl carrier protein (ACP) end products of fatty acid biosynthesis as acyl donors, but may use as well acyl-CoA derivatives, that had been formed by acyl-CoA synthetase FadD from free fatty acids [9]. The PlsY acyltransferase family is more widely distributed in bacteria and utilizes acyl-phosphate as acyl donor, which is produced from acyl-ACP by the PlsX enzyme [10]. The second acylation at the *sn*-2 position of 1-acyl-G3P to form phosphatidic acid (PA) is carried out by members of the PlsC family all of which use acyl-ACP as acyl donor [11,12]. Only PlsC acyltransferases from γ-proteobacteria may also use acyl-CoA.

In the presence of CTP, PA can be activated by the CDP-diacylglycerol (CDP-DAG) synthase CdsA [13,14], resulting in the formation of inorganic pyrophosphate (PPi) and CDP-DAG. CDP-DAG is the common precursor used for the synthesis of glycerophospholipids in bacteria. Enzymes that use CDP-DAG usually belong to the CDP-alcohol transferase family or to the PLD superfamily each displaying their characteristic protein sequence motifs as reviewed by Sohlenkamp and Geiger [15].

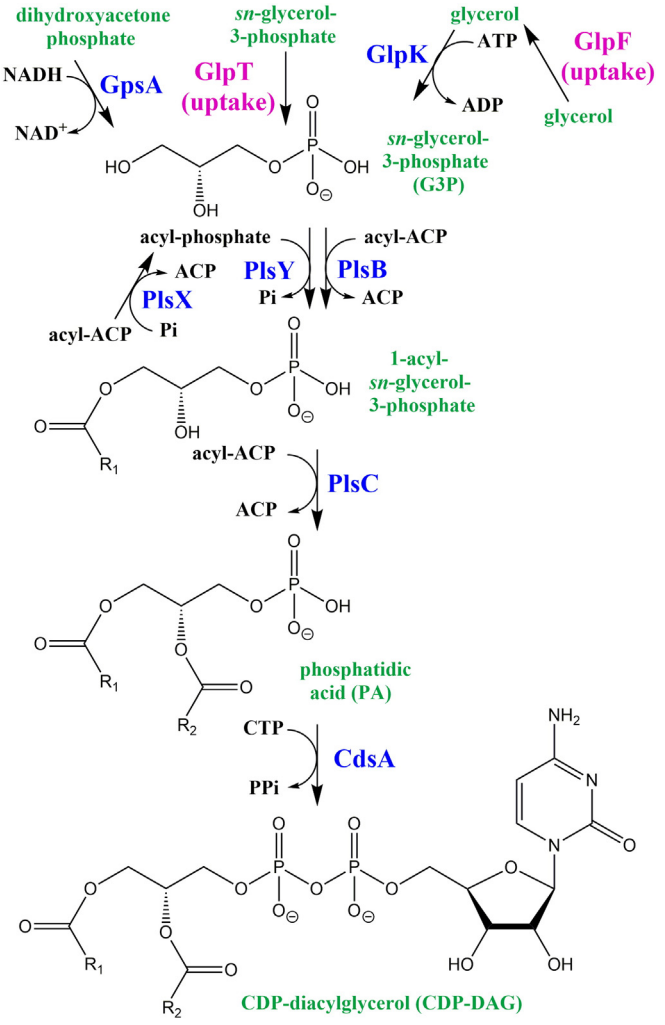

Fig. 1. Synthesis of phosphatidic acid and CDP-diacylglycerol in bacteria (for details see text). Names of enzymes are indicated in blue and of transporters in pink.

3. Diversification of glycerophospholipids with distinct head groups

Studies with the model bacterium *Escherichia coli* suggested that this organism forms only three major phospholipids. The zwitterionic phosphatidylethanolamine (PE) comprises about 75% of its membrane phospholipids whereas the anionic phosphatidylglycerol (PG) (about 20%) and cardiolipin (CL) (about 5%) contribute the remaining 25% [16], although the relative amount of CL increases as bacteria transit from exponential growth to stationary conditions. However, even in *E. coli* many more minor phosphorus-containing lipids are formed [17]. Considering that fatty acyl groups can vary in the *sn*-1 and *sn*-2 position of membrane phospholipids, due to the possible combinations, it becomes evident that the number of distinct glycerophospholipid molecules is enormous even in *E. coli* [18]. The history of the research on bacterial and eukaryotic lipid synthesis has recently been traced in an informative review [19].

3.1. Synthesis pathways for zwitterionic phospholipids

3.1.1. Biosynthesis of phosphatidylethanolamine (PE)

PE is a frequent and abundant phospholipid in Gram-negative bacteria [15]. The first step in the synthesis of PE is the condensation of CDP-DAG with serine to form phosphatidylserine (PS) catalyzed by PS synthase Pss [20]. In a second step, PS is decarboxylated by phosphatidylserine decarboxylase (Psd) leading to the formation of the zwitterionic lipid PE (Fig. 2). Pss enzymes belong to two different families: type I Pss are phospholipase D-like proteins whereas type II proteins belong to the CDP-alcohol phosphotransferase family [21]. For example, Pss from *E. coli* is a type I Pss whereas Pss from *B. subtilis* and *S. meliloti* are type II Pss [21]. Though both types of Pss enzymes are unrelated on the sequence level, they both employ CDP-DAG and L-serine as substrates and form PS and CMP as products. Whereas type I Pss is restricted to a few γ-proteobacteria, type II Pss occurs in all three domains of life [21]. The Psd gene product has been initially isolated from *E. coli* [22] and possesses a unique pyruvate prosthetic group, that is obtained by autoprocessing of the proenzyme into catalytically functional Psd [23]. Mutants deficient in *pss* or *psd* have been obtained in several bacteria (reviewed in [15]). In general, these mutants are viable under specific growth conditions and many require bivalent cations in the growth medium. Recently, Moser et al. [24] described a bifunctional cardiolipin/phosphatidylethanolamine synthase (CL/PE synthase) in the plant pathogen *Xanthomonas campestris* which catalyzes the synthesis of PE from CDP-DAG and ethanolamine (Fig. 2). This same enzyme also functions as a CL synthase and, as many bacterial CL synthases, belongs to the PLD superfamily. In eukaryotes, PE synthesis via the CDP-ethanolamine pathway has been described, but this reaction is unknown to date in prokaryotes [25].

3.1.2. Biosynthesis of phosphatidylcholine (PC)

In eukaryotes two different pathways for PC synthesis are known, the CDP-choline pathway and the *N*-methylation pathway [1]. In the CDP-choline pathway, choline is phosphorylated by choline kinase using ATP. In a second step, phosphocholine and CTP react to CDP-choline, catalyzed by CTP:phosphocholine cytidylyltransferase, and finally CDP-choline: 1,2-diacylglycerol cholinephosphotransferase (CPT) catalyzes the reaction between CDP-choline and DAG leading to the formation of PC and CMP. In the *N*-methylation pathway, PE is *N*-methylated three times leading to the formation of PC. Only few bacteria were known to be able to synthesize PC and for a long time only the *N*-methylation pathway for PC synthesis was known in Bacteria [26,27] (Fig. 2). Genes encoding a bacterial phospholipid *N*-methyltransferase (Pmt) were reported first in *R. sphaeroides* and later in *S. meliloti* [28,29]. Both Pmt's share little sequence similarity and belong to two different methyltransferase families. The similarity on amino acid level is restricted to the putative *S*-adenosylmethionine (SAM)-binding site and

Please cite this article as: I.M. López-Lara, O. Geiger, Bacterial lipid diversity, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.10.007