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Mini-review

Knowns and unknowns of membrane lipid synthesis in streptomycetes

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ABSTRACT

Bacteria belonging to the genus *Streptomyces* are among the most prolific producers of antibiotics. Research on cellular membrane biosynthesis and turnover is lagging behind in *Streptomyces* compared to related organisms like *Mycobacterium tuberculosis*. While natural products discovery in *Streptomyces* is evidently a priority in order to discover new antibiotics to combat the increase in antibiotic resistant pathogens, a better understanding of this cellular compartment should provide insights into the interplay between core and secondary metabolism. However, some of the pathways for membrane lipid biosynthesis are still incomplete. In addition, while it has become clear that remodelling of the membrane is necessary for coping with environmental stress and for morphological differentiation, the detailed mechanisms of these adaptations remain elusive. Here, we aim to provide a summary of what is known about the polar lipid composition in *Streptomyces*, the biosynthetic pathways of polar lipids, and to highlight current gaps in understanding function, dynamics and biosynthesis of these essential molecules.

1. Introduction

Bacteria belonging to the genus *Streptomyces* are among the most prolific producers of antibiotics. They form part of the class Actinobacteria, within the high G + C Gram positive bacteria. Their huge repertoire of diverse secondary metabolites has been exploited for biomedical purposes, and in addition to antibiotics, some of their natural products have found use as antifungic, antiparasitic, immunosupressant and antitumoral agents [1]. The life cycle of *Streptomyces* involves a complex morphological differentiation program akin to that of filamentous fungi, growing from a spore into a vegetative mycelium composed of branching hyphae. Upon some nutritional cues, this vegetative mycelium erects aerial hyphae which later differentiate into spore chains in a process that is coordinated with the production of antibiotics and other secondary metabolites [2]. The regulatory networks that control this developmental program continue to be the focus of extensive research in *Streptomyces* [3,4].

Lipid molecules have many roles in cellular processes and metabolism. The neutral lipid triacylglycerol (TAG) can be accumulated for energy storage, both in complex eukaryotes and in some bacteria, such as *Streptomyces* [5]. Several contributions have been made to our understanding of the biosynthesis and regulation of TAG [6–8] and fatty acids [9,10] in this genus. Polar lipids are key components of the cellular envelope, essential for the structure and functions of biological membranes. The biosynthesis and turnover of the lipids conforming the *Streptomyces* envelope is, however, much less explored than other parts of its core and secondary

Abbreviations: G3P, glycerol-3-phosphate; LPA, lyso-phosphatidic acid; PA, phosphatidic acid; CDP-DAG, cytidine diphosphate diacylglycerol; PE, phosphatidylethanolamine; PS, phosphatidylserine; PG, phosphatidylglycerol; PGP, phosphatidylglycerol-phosphate; CL, cardiolipin; MLCL, monolyso-cardiolipin; DLCL, dilyso-cardiolipin; PI, phosphatidylinositol; PIP, phosphatidylinositol-phosphate; PIMs, phosphatidylinositol mannosides; PIM_1, phosphatidylinositol monomannoside; PIM_2, phosphatidylinositol dimannoside; OL, ornithine lipid; P_i, inorganic phosphate; SQ, squalene; IPP, isopentenyl diphosphate; DMAPP, dimethylallyl diphosphate; GPP, geranyl diphosphate; FPP, farnesyl diphosphate; ABHT, aminobacteriohopanetriol; SHC, squalene-hopene cyclase.

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metabolism. Some phospholipid biosynthesis pathways have been studied in the genus *Mycobacterium*, where several essential genes involved in phospholipid synthesis have been discovered [11,12]. Recent research has also discovered essential lipids in *Streptomyces* [13] and a remarkable variability in the composition of its cytoplasmic membrane [14].

In this minireview we describe the current knowledge on the diversity of polar lipids present in streptomycetes, their biosynthesis, dynamics and regulation, with emphasis on missing key pieces of information yet to be uncovered.

2. Phospholipid biosynthesis

2.1. Synthesis of phosphatidic acid and cytidine diphosphate diacylglycerol

The first step in phospholipid biosynthesis is the acylation of glycerol-3-phosphate (G3P) to produce lyso-phosphatidic acid (LPA, also known as 1-acyl-*sn*-glycerol-3-phosphate) (Fig. 1). LPA can be formed by two different pathways. The acyltransferase PlsB [15] was first identified in *E. coli* and is apparently mostly restricted to a few families of γ-proteobacteria. This enzyme transfers an acyl chain from acyl coenzyme A to G3P to form LPA. A second pathway, much more widespread in bacteria, involves two separate reactions through the enzymes PlsX and PlsY. PlsX converts acyl-ACP to acyl-phosphate, which is subsequently used by the glycerol-phosphate acyltransferase PlsY [16]. Interestingly, *Streptomyces* genomes apparently lack both of these pathways, so the first step in phospholipid synthesis is unresolved. This seems to be the case for the majority of bacteria in the order Actinomycetales, since only genera closely related to *Mycobacterium* seem to have homologues to PlsB.

Phosphatidic acid (PA) is synthesized via a second acylation of G3P. This reaction is performed by the LPA acyltransferase PlsC [17], of which there are several homologues in the genome of

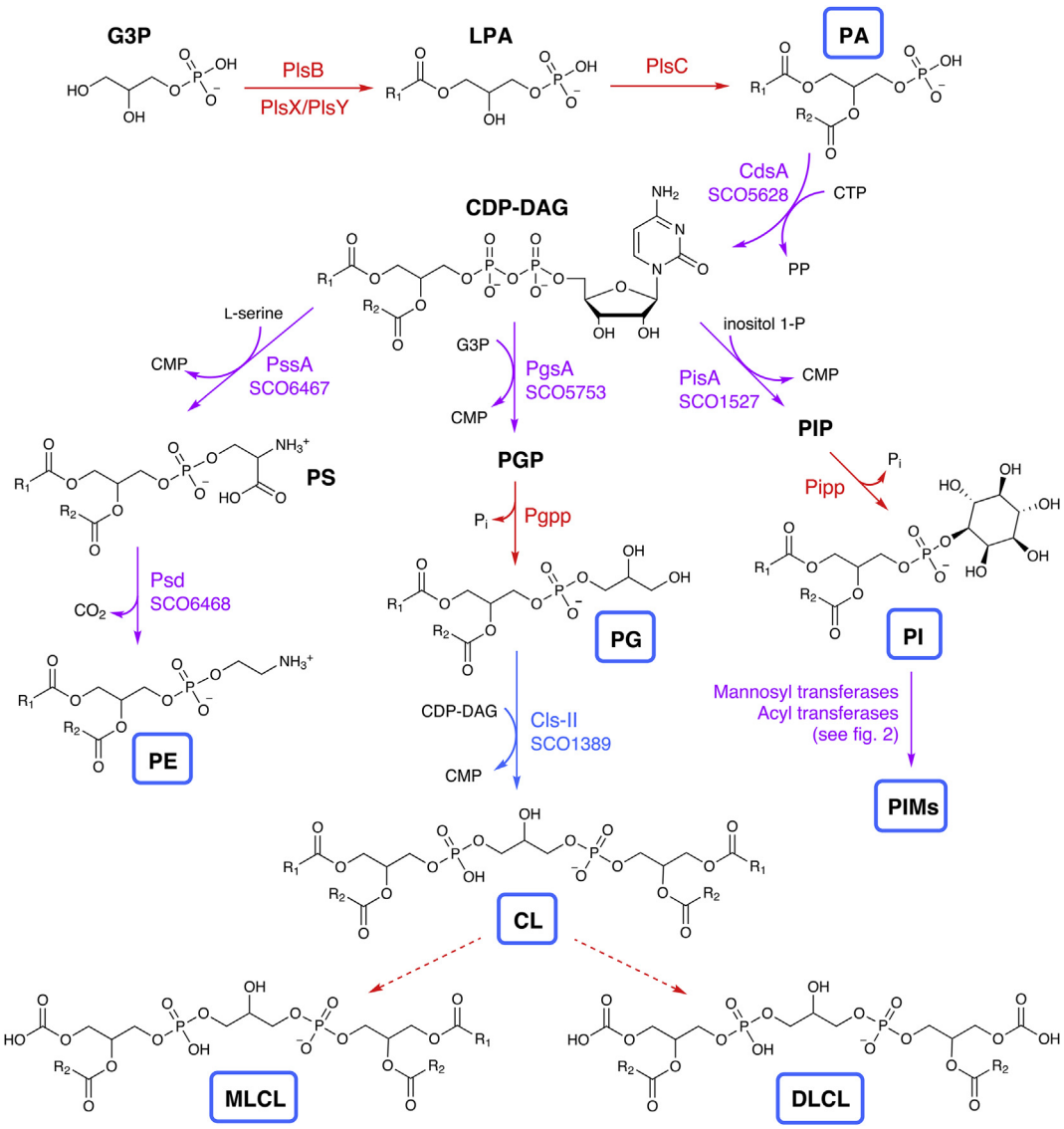

Fig. 1. Phospholipid biosynthetic pathways in *Streptomyces*. Parts of the biosynthetic pathway with experimental evidence are shown in blue, those with only bioinformatic predictions are shown in purple, and the reactions for which there is not enough evidence for any gene associated with them are shown in red. Phospholipids that have been identified in *Streptomyces* lipid extracts are highlighted in blue rectangles. G3P, glycerol-3-phosphate; LPA, lyso-phosphatidic acid; PA, phosphatidic acid; CDP-DAG, cytidine diphosphate diacylglycerol; PS, phosphatidylserine; PE, phosphatidylethanolamine; PGP, phosphatidylglycerol-phosphate; PG, phosphatidylglycerol; CL, cardiolipin; MLCL, monolyso-cardiolipin; DLCL, dilyso-cardiolipin; PIP, phosphatidylinositol-phosphate; PI, phosphatidylinositol; PIMs, phosphatidylinositol mannosides.

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