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Review

Bacterial lipids: Metabolism and membrane homeostasis

Joshua B. Parsons, Charles O. Rock *

Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA

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ABSTRACT

Membrane lipid homeostasis is a vital facet of bacterial cell physiology. For decades, research in bacterial lipid synthesis was largely confined to the *Escherichia coli* model system. This basic research provided a blueprint for the biochemistry of lipid metabolism that has largely defined the individual steps in bacterial fatty acid and phospholipids synthesis. The advent of genomic sequencing has revealed a surprising amount of diversity in the genes, enzymes and genetic organization of the components responsible for bacterial lipid synthesis. Although the chemical steps in fatty acid synthesis are largely conserved in bacteria, there are surprising differences in the structure and cofactor requirements for the enzymes that perform these reactions in Gram-positive and Gram-negative bacteria. This review summarizes how the explosion of new information on the diversity of biochemical and genetic regulatory mechanisms has impacted our understanding of bacterial lipid homeostasis. The potential and problems of developing therapeutics that block pathogen phospholipid synthesis are explored and evaluated. The study of bacterial lipid metabolism continues to be a rich source for new biochemistry that underlies the variety and adaptability of bacterial life styles.

Contents

* Corresponding author. Tel.: +1 9015953491.
E-mail address: charles.rock@stjude.org (C.O. Rock).

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1. Introduction

Bacterial lipid metabolism has long had a significant impact on the understanding of the basic lipid metabolic pathways, enzyme mechanisms and transcriptional regulation. The early work in the *Escherichia coli* system jump-started the investigation of fatty acid and phospholipid synthesis. A recent review by Dowhan [1] recounts these early days of discovery in bacterial lipid metabolism. For decades, *E. coli* was considered the paradigm for bacterial metabolism; however, the advent of the genomic era revealed that genes and enzymes of lipid metabolism painstakingly investigated in *E. coli* are not common to all bacteria. This realization has accelerated research into the great diversity in pathways, and fatty acid and phospholipid structures that occur in nature. This review attempts to capture and organize this diversity to provide an overview of lipid metabolism in prokaryotes as it stands today.

2. Biochemistry of Bacterial Lipid Synthesis

2.1. The FASII initiation module

The function of the initiation module of FASII is to produce the primer and the building blocks to feed the elongation module (Fig. 1). The acetyl-CoA carboxylase (ACC) performs the first committed step in bacterial phospholipid synthesis to generate malonyl-coenzyme A (malonyl-CoA) through the carboxylation of acetyl-CoA [2–4]. In order to be recognized by the FASII enzymes, the malonate group from malonyl-CoA must be transferred to acyl carrier protein (ACP) by FabD [5]. The condensation of malonyl-ACP with a short-chain acyl-CoA (C_2–C_5) by FabH initiates the elongation cycle [6–8]. The malonyl-ACP generated by the ACC and FabD is also used by the elongation cycle to extend the growing fatty acid chain, illustrating how crucial ACC activity is to maintaining the optimum rate of membrane phospholipid synthesis. Every condensation reaction performed by FabH will result in the production of a new fatty acid to expand the membrane. Consequently, the initiation module is ideally positioned for biochemical and genetic regulation of the amount of fatty acids produced and speed at which they are manufactured.

2.1.1. Acetyl-CoA carboxylase

The acetyl-CoA carboxylase enzyme is present in animals, plants, fungi and bacteria. In bacteria, the ACC is a multisubunit complex consisting of a biotin carboxylase (AccC), biotin carboxyl carrier protein (AccB, also known as BCCP) and a carboxyltransferase (AccAD). AccB and AccC exist as homodimers while AccAD is a heterotetramer [3,9,10]. In the cell, ACC is likely a multimeric complex of these four subunits; however, the complex readily dissociates following cell disruption leaving only the two ACC half reactions that can be measured. The first half reaction catalyzes the ATP-dependent carboxylation of biotin on AccB by AccC [11,12]. The carboxylation of free biotin or biotin analogs is an extremely inefficient reaction, and maximum rates required biotin to be covalently attached to a lysine residue of biotin carboxyl carrier protein (AccB) [11,13]. In the second half reaction, the carboxyl group is transferred from carboxyl-AccB to acetyl-CoA by AccAD. The two half-reactions can be assayed individually but reconstituting the complete ACC reaction is more challenging [14,15]. High concentrations of each purified subunit are required to reach a threshold concentration for the catalytically active complex to form in vitro [11,12,16]. The genetic organization of the four *acc* genes differs between organisms. In *E. coli* and *Staphylococcus aureus*, the *accAD* and *accBC* genes are organized in operons located at different regions of the chromosome [9]. In *Streptococcus pneumoniae*, the *acc* genes are located adjacent to each other in a transcriptional unit that also contains the other FASII genes [17]. Evidence that the ACC governs the quantity of fatty acid produced by the cell was provided by a study involving the overexpression of *accABCD* in *E. coli.* Maintaining a normal lipid to protein ratio is critical for homeostasis, therefore the authors devised a means to uncouple FASII from phospholipid synthesis and excrete the excess fatty acids from the cell. The *acc* genes were overexpressed in combination with a soluble acyl-ACP thioesterase to uncouple FASII from membrane synthesis resulting in 5–6-fold increase in fatty acid

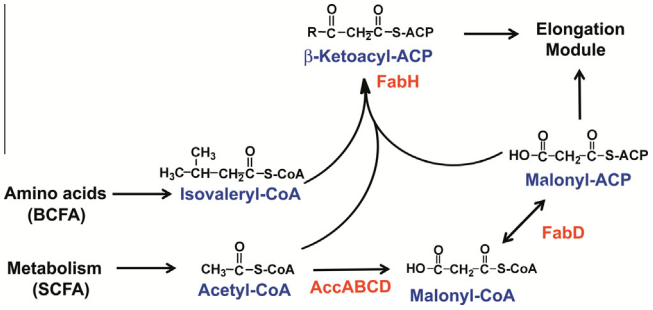

Fig. 1. The initiation module of type II fatty acid synthesis. The priming reaction for the elongation cycle is performed by the by the initiating condensing enzyme, FabH, which condenses an acyl-CoA with malonyl-ACP. In bacteria that produce straight chain fatty acids (SCFA), acetyl-CoA is employed. Bacteria producing branched-chain fatty acids (BCFA) utilize an amino acid derived branched chain acyl-CoA precursor. Malonyl-CoA is formed by acetyl-CoA carboxylase, which is composed of four different protein subunits encoded by separate genes (AccABCD). Malonyl-ACP is formed by the transacylase, FadD.