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Review

Exogenous fatty acid metabolism in bacteria

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ABSTRACT

Bacterial type II fatty acid synthesis (FASII) is a target for novel antibiotic development. All bacteria encode for mechanisms to incorporate exogenous fatty acids, and some bacteria can use exogenous fatty acids to bypass FASII inhibition. Bacteria encode three different mechanisms for activating exogenous fatty acids for incorporation into phospholipid synthesis. Exogenous fatty acids are converted into acyl-CoA in Gammaproteobacteria such as *E. coli*. Acyl-CoA molecules constitute a separate pool from endogenously synthesized acyl-ACP. Acyl-CoA can be used for phospholipid synthesis or broken down by β-oxidation, but cannot be used for lipopolysaccharide synthesis. Exogenous fatty acids are converted into acyl-ACP in some Gram-negative bacteria. The resulting acyl-ACP undergoes the same fates as endogenously synthesized acyl-ACP. Exogenous fatty acids are converted into acyl-phosphates in Gram-positive bacteria, and can be used for phospholipid synthesis or become acyl-ACP. Only the order Lactobacillales can use exogenous fatty acids to bypass FASII inhibition. FASII shuts down completely in presence of exogenous fatty acids in Lactobacillales, allowing Lactobacillales to synthesize phospholipids entirely from exogenous fatty acids. Inhibition of FASII cannot be bypassed in other bacteria because FASII is only partially down-regulated in presence of exogenous fatty acid or FASII is required to synthesize essential metabolites such as β-hydroxyacyl-ACP. Certain selective pressures such as FASII inhibition or growth in biofilms can select for naturally occurring one step mutations that attenuate endogenous fatty acid synthesis. Although attempts have been made to estimate the natural prevalence of these mutants, culture-independent metagenomic methods would provide a better estimate.

Contents

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1. Introduction

Phospholipids are major components making the essential cellular membrane that forms the boundary between the organism and the environment [1]. Phosphatidic acid, the precursor to all phospholipid species, is synthesized through two successive acylation reactions of glycerol-3-phosphate (G3P) using acyl-acyl carrier protein (ACP) synthesized by the bacterial type II fatty acid synthesis system (FASII) (Fig. 1) [2]. Due to differences between FASII and the monofunctional mammalian type I fatty acid synthase [3], targeting FASII enzymes for novel antibiotic therapeutics is an active area of research [4–7]. However, all bacteria characterized to date can assimilate exogenous fatty acids [8–12], but only some species can bypass inhibition of FASII by incorporating exogenous fatty acids [13]. Several FASII inhibitors are currently in clinical development [14–20], making understanding the mechanism of exogenous fatty acid activation for phospholipid synthesis and whether exogenous fatty acids can bypass FASII inhibition in pathogenic bacterial species an important area of research. This review will summarize the pathways for the incorporation of exogenous fatty acids into phospholipids and whether exogenous fatty acids can bypass the inhibition of endogenous fatty acid synthesis in those species.

2. Pathways for exogenous fatty acid incorporation

Fatty acid synthesis is an energy and material intensive process (Fig. 1) in phospholipid synthesis and the incorporation of useable exogenous fatty acids saves energy and metabolic building materials. The synthesis of the 16 carbon, saturated palmitoyl-CoA requires 8 acetyl-CoA molecules, 14 NADPH reducing equivalents, and the hydrolysis of 7 ATP molecules [1]. Two acyl-ACP molecules are used in successive acylation reactions to synthesize phosphatidic acid, the precursor to all bacterial phospholipid species [2]. There are two major types of acyltransferase systems found in bacteria. The PlsB pathway found in *E. coli* and other Gammaproteobacteria acylates the G3P using acyl-ACP or acyl-CoA [21–23]. The PlsX/PlsY pathway found in all other characterized bacterial taxa acylates G3P using an acyl-phosphate derived from acyl-ACP via PlsX [24,25]. PlsC acylates the resulting lysophosphatidic acid using acyl-ACP in both pathways [26,27]. Further details of these two pathways can be found in a recent review [2]. This review will focus on how the exogenous fatty acid activation systems present fatty acids to the acyltransferases.

The energy and material savings gained from being able to use exogenous fatty acids (when the correct acyl chain species are available) in lieu of endogenous synthesis suggests why all bacteria characterized to date encode for some mechanism to incorporate exogenous fatty acids [2]. However, the acyl chain composition of the phospholipid controls the membrane fluidity and function [28–32], so bacteria must balance the energy savings from incorporating exogenous fatty acids with synthesizing enough fatty acids endogenously to ensure the proper membrane biophysical properties. There are three characterized mechanisms for incorporating exogenous fatty acids: acyl-CoA synthetase, acyl-ACP synthetase, and fatty acid kinase. The acyl-CoA synthetase was first discovered in *E. coli* and found in Gammaproteobacteria bacteria [12]. Acyl-CoA synthetases are also found in mammalian lipid synthesis, and is an essential component because the free fatty acids generated by mammalian fatty acid synthase must be converted into acyl-CoA for phospholipid synthesis [33]. Acyl-ACP synthetase was the second mechanism discovered [34,35]. Acyl-ACP synthetases belong in the

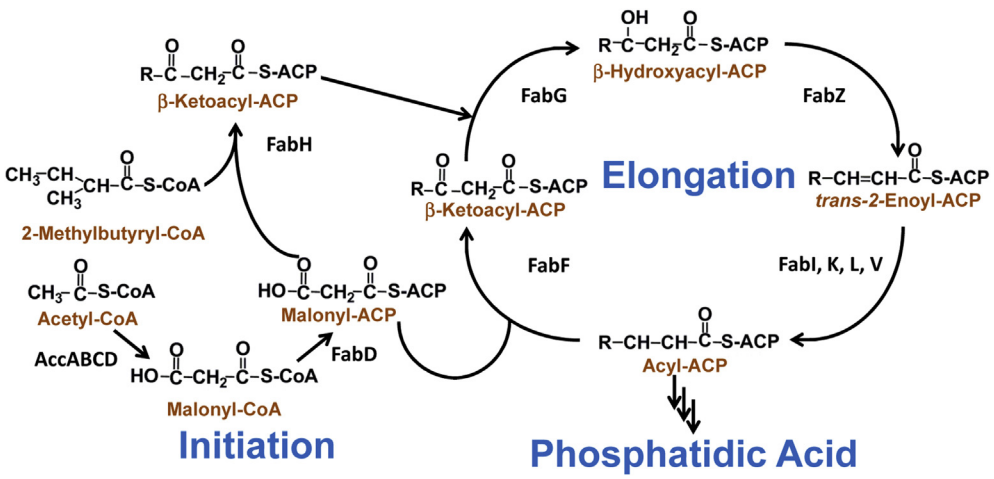

Fig. 1. The core enzymes in bacterial type II fatty acid synthesis. The acetyl-CoA carboxylase enzyme complex (AccABCD) converts aceyl-CoA into malonyl-CoA, which is in turn converted into malonyl-ACP by the malonyl-CoA:ACP transacylase (FabD). The β-ketoacyl-ACP synthase III (FabH) catalyzes the condensation of malonyl-ACP with either acetyl-CoA or 2-methylbutyryl-CoA to form β-ketoacyl-ACP and initiate straight- or branched-chain *anteiso* fatty acid synthesis. The β-ketoacyl-ACP is reduced by β-ketoacyl-ACP reductase (FabG) to make β-hydroxyacyl-ACP. β-hydroxyacyl-ACP of the appropriate length is used for lipopolysaccharide synthesis in Gram-negative bacteria. β-hydroxyacyl-ACP is dehydrated by β-hydroxyacyl-ACP dehydratase (FabZ) to make *trans*-2-enoyl-ACP. The *trans*-2-enoyl-ACP is reduced by enoyl-ACP reductase (FabI) into acyl-ACP. Acyl-ACP of the appropriate length can be used for phospholipid synthesis. Acyl-ACP can also be lengthened by two carbons through condensation with malonyl-ACP by β-ketoacyl-ACP synthase II (FabF) to make β-ketoacyl-ACP, which can undergo another elongation cycle by FabG, FabZ, FabI, and FabF. The bacterial FASII enzymes are soluble, discrete, and monofunctional, in contrast to the multifunctional mammalian fatty acid synthase. There are multiple isoforms of the enoyl-ACP reductase enzyme (FabK, FabL, and FabV). Additional enzymes interact with the FASII intermediates to synthesize unsaturated fatty acid and lipoic acid. Please refer to reviews for more details in FASII operation [1,105].

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