GLOBAL REGULATION OF FATTY ACID BIOSYNTHESIS IN GRAM-POSITIVE BACTERIA

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Fatty acids and their derivatives play essential roles in all living organisms as components of membranes and source of metabolic energy. Biosynthesis of these compounds involves repeated cycles of condensation, reduction and dehydration of carbon-carbon linkages, which are carried out by a single multifunctional polypeptide (type I systems) in higher eukaryotes and by discrete proteins (type II systems) in bacterial cells and plant chloroplasts. A tight regulation of lipid homeostasis is essential to assure the stable compositions of biological membranes, but the underlying regulatory mechanisms are largely unknown. We have recently shown that malonyl-CoA (mCoA), an essential intermediate in fatty acid synthesis, is also a direct and specific inducer of *Bacillus subtilis* FapR, a conserved transcriptional repressor that regulates the expression of several genes involved in bacterial fatty acid and phospholipid synthesis [ref 1]. The crystal structures of the effector-binding domain of FapR from both *B. subtilis* and the human pathogen *Staphilococcus aureus* reveals a homodimeric protein with a thioesterase-like “hot-dog” fold. Binding of mCoA promotes a disorder-to-order transition, which transforms an open ligand-binding groove into a long tunnel occupied by the effector molecule in the complex. This ligand-induced modification propagates to the helix-turn-helix motifs, impairing their productive association for DNA binding. Structure-based mutations that disrupt the FapR-mCoA interaction prevent DNA-binding regulation and result in a lethal phenotype in *B. subtilis,* suggesting that this homeostatic pathway can represent a promising target for novel chemotherapeutic agents against Gram-positive pathogens.

[1] Schujman *et al, EMBO Journal*, **25**:4074-4083 (2006).