Is There an Answer?

Is There an Answer? is intended to serve as a forum in which readers to IUBMB Life may pose questions of the type that intrigue biochemists but for which there may be no obvious answer or one may be available but not widely known or easily accessible.

Readers are invited to e-mail f.vella@sasktel.net if they have questions to contribute or if they can provide answers to questions that are provided here from time to time. In the latter case, instructions will be sent to interested readers. Answers should be, whenever possible, evidence-based and provide relevant references. — Frank Vella

Q & A

Question: Is the fatty acid synthesis pathway a good target for anti-malarial therapy?
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Proteins and nucleic acids may be the basic building blocks of organisms, but without fatty acids, the scaffold of life would be incomplete. Fatty acids are the essential components of phospholipids and sphingolipids that make up cellular and intracellular membranes, and cofactors, pigments, signaling molecules, etc. Fatty acids are synthesized from simple precursors by all organisms, save for a few like the mycoplasmas, which acquire them from their host (1). So, on to center stage! The action is where the fatty acids are synthesized!!!

The reactions of fatty acid synthesis are catalyzed by a single multi-domain polypeptide in the type I pathway, which is present in the cytosol of eukaryotes including man, fungi and some mycobacteria. In contrast, individual enzyme molecules that catalyze each of the reactions characterize the type II pathway that is widespread in bacteria, and present in algal and plant plastids, and yeast mitochondria. While the type I pathway contains Acyl Carrier Protein (ACP), the central player in this pathway as an integral component, ACP is a distinct protein in the type II pathway. Both the ACPs, however, share significant structural homology and analogous biochemical properties, and the ACP domain of the type I fatty acid synthase (FAS) can in fact be recognized efficiently as a substrate by systems with type II fatty acid biosynthesis (2). Though corresponding information is not available for the other domains of FAS, the differential effect of inhibitors like triclosan on the two systems suggest that they do differ in some aspect.

Fatty acid synthesis comprises two major phases – initiation and elongation (Fig.1). Initiation requires acetyl-CoA carboxylase (ACC), which catalyzes the synthesis of malonyl-CoA from acetyl-CoA and carbon dioxide. This is the committed step for fatty acid synthesis. Malonyl-CoA is transacylated to malonyl-ACP by malonyl-CoA:ACP transacylase or FabD. The elongation phase comprises a condensation, a dehydration and two reduction reactions. Elongation is initiated by the condensation of malonyl-ACP and acetyl-CoA to β-ketoacyl-ACP by β-ketoacyl-ACP synthase III or FabH. This is reduced to β-hydroxyacyl-ACP by β-ketoacyl-ACP reductase or FabG. β-hydroxyacyl-ACP is dehydrogenated to enoyl-ACP by β-hydroxyacyl-ACP dehydrase or FabZ, and enoyl-ACP is finally reduced to butyryl-ACP by enoyl-ACP reductase or FabI. Butyryl-ACP is then elongated by consecutive addition of -(CH2)- groups donated by malonyl-ACP by the condensing enzyme β-ketoacyl-ACP synthase I/II or FabB/F and subsequent reactions catalyzed by FabG, FabZ and FabI till fatty acids of chain length C12 to C16 are produced. The fatty acid is then cleaved from the ACP, modified according to requirement and utilized.

More than three centuries after the discovery of quinine, the first antimalarial, a permanent solution to the debilitating disease, malaria, one of the most dreaded scourges of the tropics, remains elusive. Malaria afflicts three hundred million to five hundred million people, and claims more than a million lives every year (3). The human malarial parasite, Plasmodium falciparum, was claimed to meet its lipid requirements by scavenging from its host cell – the human erythrocyte (4, 5). This widely held view was no longer tenable with the demonstration of the entire fatty acid synthesis pathway in...
Evidence for this included the identification of nucleus-encoded apicoplast-targeted genes for three enzymes of this pathway, the incorporation of $^{14}$C-acetate into the malarial parasite $(6, 8–12)$. Triclosan has in fact been a widely used topical antibacterial agent in several off-the-counter dental, dermatological and other applications for more than thirty years, with no evidence of resistant microbes in the wild to its credit, though laboratory strains of triclosan-resistant microbes have been reported $(20, 21)$. Inhibition of regulatory enzymes of fatty acid biosynthesis, as yet unexplored, could potentially unravel new realms for therapeutics and antimalarial agents. The icing on the cake is that inhibition of fatty acid synthesis in $Plasmodium$ leads to rapid death of the parasite unlike the delayed death evoked by several antibacterial agents that target the plastid $(22)$. We seem to have finally discovered the malarial parasite’s Achilles’ heel. It would definitely be worthwhile to develop a new armament of agents that target this chink in the parasite’s armor – its fatty acid biosynthesis pathway.

**References**


