Yeast Type I Fatty Acid Synthase Constructs Fatty Acids in a Multi-site Enclosed Reaction Chamber

The crystal structure of yeast fatty acid synthase, a cellular machine with eight active sites working together.
I.B. Lomakin, Y. Xiong, and T.A. Steitz,
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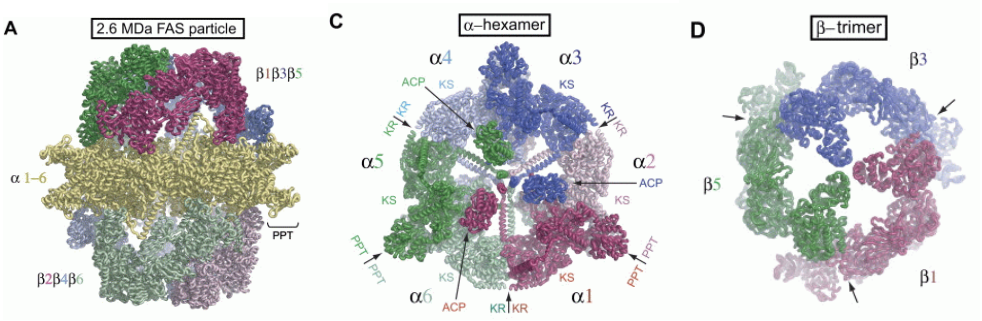
Fatty acids, used for energy storage as well as constructing cell membranes, are essential to almost all organisms. Their synthesis is carried out by fatty acid synthase (FAS), using a series of initiation, elongation, and termination steps which are highly conserved across species. Although the reactions catalyzed are the same, FAS's come in two classes: type I (found in animals, fungi, and some bacteria) is a multimer of one or two types of polypeptide chain, with multiple active sites on each chain; type II (from other bacteria, plants, and mitochondria) is a set of several small independent proteins, one for each step of the synthesis. Yeast FAS is a 2.6 MDa type I structure, containing 6 α and 6 β chains.

Biochemical experiments, electron microscopy, and a 5 Å crystal structure of a fungal type I FAS (also $\alpha_6\beta_6$) indicated that each αβ unit contains 8 active sites, at which all the reactions needed to synthesize a fatty acid are carried out, and that the reactions occur in a confined space inside the FAS complex. However, details of the active sites, and of the paths followed by the reacting molecules, were lacking.

The Steitz group has now determined the yeast FAS structure at 4 Å resolution, using molecular replacement. The starting model had been constructed (by another group) by fitting the backbone of homologous domains into the low resolution fungal FAS envelope. Because of the high solvent content and 9-fold non-crystallographic symmetry, density modification techniques were extremely successful in improving the electron density map, and it was possible to confidently model backbone for 1687 out of the 1887 amino acids, as well as about half the sidechains.

The figure shows how the α chains are arranged in a central wheel-shaped structure, with a dome of 3 β chains on each side forming a triple reaction chamber between dome and wheel. The ACP domain, which is the N-terminal portion of the α chain, is attached to the rest of the chain by a flexible linker, allowing it to move around within the chamber, transferring the growing fatty acid from one reaction site to another: the priming and initiation AT site on the β chain, KS and KR sites on the α chain, DH and ER sites on β. During elongation the fatty acid cycles between KS, KR, DH, and ER. The final site, MPT on the β chain, terminates growth. The PPT domain is used to activate FAS by modifying ACP; this must involve a major conformational change, as PPT is far from ACP in this structure.



Overall structure of yeast FAS complex: (A) side view of the whole complex, (C) top view of the central "wheel" structure, composed of 6 α subunits, (D) top view of one of the "dome" structures, comprising 3 β chains.