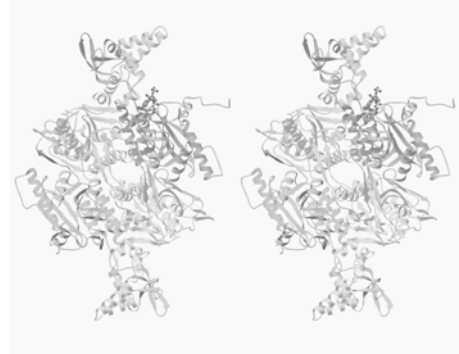


W0201

Structural Basis for the Inhibition of the Carboxyltransferase Domain of Acetyl-Coenzyme A Carboxylase.
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Acetyl-CoA carboxylases (ACCs) are required for the biosynthesis and oxidation of long-chain fatty acids. They are targets for therapeutics against obesity and diabetes, and several commercial herbicides function by inhibiting its carboxyltransferase (CT) domain. We expressed and purified the CT domain of yeast ACC, which constitutes the 90-KD fragment at the C terminus of the protein. The structure of the free enzyme was determined at 2.7 Å resolution by the seleno-methionyl single-wavelength anomalous diffraction (SAD) method (1). The structure of CT in complex with CoA was determined at 2.7 Å resolution from a crystal grown in the presence of 2 mM acetyl-CoA. The crystal structures show that CT domain comprises two subdomains, N and C domains, both with folds belonging to the crotonase/ClpP superfamily. The active site is at the interface of a dimer of the CT domain. The CoA molecule is mostly associated with the N domain of one molecule in the dimer. Mutagenesis and kinetic studies define the functional roles of conserved residues in the active site. We have recently determined the crystal structures of the CT domain in complex with the herbicide inhibitors, as well as other potent inhibitors. The structural information should prove especially useful in the design and optimization of inhibitors against the CT domains of these important therapeutic targets.



1. H. Zhang, Z. Yang, Y. Shen, L. Tong. *Science*, 299, 2064-2067, (2003).