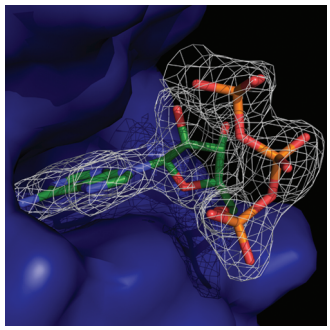
In this ISSUE

Enzymatic Evolution

How proteins acquired enzymatic activity is a fascinating aspect of evolutionary biology. Examination of proteins from extinct animals, along with innovative protein engineering methods, have provided insight into the evolution of new catalytic activity, but how the first enzymes emerged remains a mystery. Using *in vitro* selection to create a novel synthetic ATP-binding protein, Simmons *et al.* (DOI: 10.1021/cb900109w) unexpectedly discover that the protein is able to hydrolyze ATP to ADP.

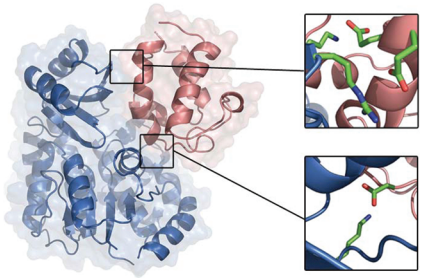
Starting with a random pool of protein sequences, four families of proteins capable of binding ATP were identified. X-ray crystallography of an optimized variant from one of the families revealed a novel nucleotide binding fold, and surprisingly, the presence of ADP in the binding site instead of ATP. Further investigation indicated that the protein binds ATP in an unusual bent conformation, which with the help of a water molecule may facilitate the hydrolysis reaction. This study points to such constrained ligand binding geometries as a possible mechanism for the evolution of enzymatic functions.



Answers to the MCAT

Acyl carrier proteins (ACPs) are critical components of both fatty acid and polyketide synthesis, as they shuttle intermediates along the biosynthetic pathway to the appropriate enzymes. Malonyl groups are added to ACPs by malonyl coenzyme A-ACP transacylase (MCAT), but it is unclear whether fatty acid synthase (FAS) ACPs and polyketide synthase (PKS) ACPs interact with MCAT in the same way. Now, Arthur *et al.* (DOI: 10.1021/cb900099e) report the structural characterization of a bacterial FAS ACP binding to MCAT, elucidating key features of the interaction that distinguish it from the PKS ACP-MCAT interaction.

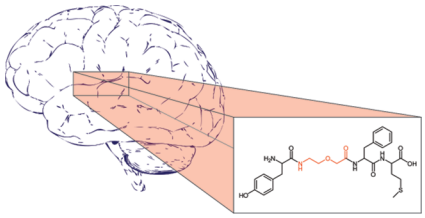
Nuclear magnetic resonance studies and mutagenesis experiments indicated that certain conserved negatively charged residues on helix II of the FAS ACP interact with specific positively charged residues in the MCAT active site. Notably, mutagenesis of analogous residues on the PKS ACP did not affect MCAT binding, suggesting that the PKS ACP may utilize a distinct mechanism to interact with MCAT. Precise characterization of these interactions not only furthers our understanding of these complex biosynthetic pathways but could facilitate the bioengineering of novel enzymes capable of producing fatty acids and polyketides with unique structures.



Seizing Neuropeptide Activity

The endogenous opioid neuropeptide Met-enkephalin can control both pain and seizures, making its mechanism of action an intriguing companion to its therapeutic relevance. Many strategies have been developed to improve the pharmacological properties of bioactive peptides and probe their function, including replacing nonessential amino acid residues with nonpeptide backbone spacers. Now, Lee *et al.* (DOI: 10.1021/cb900045c) generate backbone spacer-containing analogues of Met-enkephalin and unveil two quite unexpected findings.

The Met-enkephalin analogues were created by replacing a single peptide bond between two glycine residues with various spacer molecules. The first surprise was that the affinity of the analogues for the opioid receptors was dramatically reduced; molecular modeling studies indicate that the loss of a single hydrogen bond is responsible. Equally surprising, however, was that the analogues retained potent anticonvulsant and antinociceptive activity. Additional mechanistic studies suggest the existence of a novel signaling pathway for seizure control that does not involve opioid receptors.



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