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Publication

1EFR: Bovine Mitochondrial F1-Atpase Complexed With The Peptide Antibiotic Efrapeptin

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In the previously determined structure of mitochondrial F1-ATPase determined with crystals grown in the presence of adenylyl-imidodiphosphate (AMP-PNP) and ADP, the three catalytic beta-subunits have different conformations and nucleotide occupancies. AMP-PNP and ADP are bound to subunits beta TP and beta DP, respectively, and the third beta-subunit (beta E) has no bound nucleotide. The efrapeptins are a closely related family of modified linear peptides containing 15 amino acids that inhibit both ATP synthesis and hydrolysis by binding to the F1 catalytic domain of F1F0-ATP synthase. In crystals of F1-ATPase grown in the presence of both nucleotides and inhibitor, efrapeptin is bound to a unique site in the central cavity of the enzyme. Its binding is associated with small structural changes in side chains of F1-ATPase around the binding pocket. Efrapeptin makes hydrophobic contacts with the alpha-helical structure in the gamma-subunit, which traverses the cavity, and with subunit beta E and the two adjacent alpha-subunits. Two intermolecular hydrogen bonds could also form. Intramolecular hydrogen bonds probably help to stabilize efrapeptin's two domains (residues 1-6 and 9-15, respectively), which are connected by a flexible region (beta Ala-7 and Gly-8). Efrapeptin appears to inhibit F1-ATPase by blocking the conversion of subunit beta E to a nucleotide binding conformation, as would be required by an enzyme mechanism involving cyclic interconversion of catalytic sites.
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