Structural Studies of Human ATP-Specific Succinyl-CoA Synthetase

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Succinyl-CoA synthetase (SCS) catalyzes the only substrate level phosphorylation in the citric acid cycle: Succinyl-CoA + NDP ⇌ Succinate + CoA + NTP in the presence of magnesium ions. In mammals, SCS is a heterodimer with α and β subunits and nucleotide-specific isoforms of SCS exist: one is ATP-specific SCS (ATPSCS) and the other one is GTP-specific SCS (GTPSCS). ATPSCS is coded by genes *SUCLG1* and *SUCLA2* and GTPSCS is coded by genes *SUCLG1* and *SUCLG2*. *SUCLG1* codes for the common α subunit. The specificity of SCS for either ATP/ADP or GTP/GDP is determined by the β subunit (1). Deleterious mutation in the gene *SUCLA2* has been reported to cause diseases, such as encephalomyopathy and mitochondrial DNA depletion (2), and mutations in the genes *SUCLG1* and *SUCLA2* led to elevated levels of methylmalonic acid (3). The structures of GTPSCS and its complexes have been well studied over the decades. But there is no structure of ATPSCS or its complexes in the Protein Data Bank. Knowing the structure of the complex of ATPSCS with ATP-Mg^{2+} will be helpful in further understanding the mechanism of the SCS-catalyzed reaction.

Previous studies of full length human ATPSCS did not succeed in obtaining high resolution structures. A study of truncated human ATPSCS, with only the ATP-binding domain (Abd-ATPSCS), was proposed in order to reveal the interactions between ATPSCS and ATP- Mg^{2+}. Abd-ATPSCS was produced in *E. coli* BL21(DE3) and purified through a three-step chromatographic purification. Abd-ATPSCS was co-crystallized with ATP and magnesium ions at a high concentration of polyethylene glycol 3350. The crystal diffracted to ~2.8 Å.

References:

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