Crystal Structures of Two Domains of Bifunctional Enzyme: Human PAPS Synthetase

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PAPS synthetase is the sole enzyme that catalyzes synthesis of PAPS (3'phospoadenosine 5'-phosphosulfatate), which is the ultimate donor of sulfate in higher organisms. PAPS synthesis is a two-step process. In the first step, APS (adenosine 5'-phosphosulfate) is generated from inorganic sulfate and ATP. In the second reaction, APS is phosphorylated on 3'-OH of its sugar ring to yield PAPS molecule. In the lower organisms, these reactions are catalyzed by two separate enzymes ATP sulfurylase and APS kinase, respectively. In humans both activities are present on single polypeptide chain giving bifunctional PAPS synthetase. We have done extensive structural analysis to understand what are the implications of having both activities on one polypeptide chain. Is product of first reaction directly transferred to the active site of the second reaction? Are the two reactions coordinated? If so, how two active sites communicate?

Here we report 2.1 Å crystal structures of ATP sulfurylase domain of human PAPS synthetase in complex with its product APS refined to R_{work}=18% and R_{free}=21%; 2.1 Å crystal structure of APS kinase domain of human PAPS synthetase in complex with its substrate APS refined to R_{work}=25% and R_{free}=29% and another 1.9 Å crystal structure of the same domain in complex with its products PAPS and ADP refined to R_{work}=20% and R_{free}=24%. Our structures are do not support an enclosed channel between the two active sites but allow for communication between the domains induced by conformational changes upon substrate binding and catalysis. In addition, our structures explain strong inhibitory effect of APS on APS kinase.

Keywords: PAPS synthetase, ATP sulfurylase, APS kinase