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Biophysical Studies of Function and Stability in Adenylosuccinate Lyase STEPHEN RAY, NATHAN DUVAL, TERRY WILKINSON II, SEAN SHAHEEN, KINSHUK GHOSH, DAVID PATTERSON, University of Denver — Adenylosuccinate Lyase (ADSL) is a homotetrameric protein with four active sites that accommodate two reactions in the de novo purine biosynthesis pathway. It catalyzes the conversion of SAICAR to AICAR and AMPS to AMP. Point mutations in the gene encoding the protein ADSL lead to ADSL deficiency, a disorder characterized by serious neurological and physiological symptoms. Two leading hypotheses regarding the pathogenesis are "Loss of Function" or "Gain in Toxic Function." These hypotheses can be related to the reduction of either the enzyme kinetics or the stability of the tetramer structure. Enzymatic studies can be used to provide a quantitative measure of the extent to which the enzyme acts on its designated substrates, SAICAR and AMPS. Recent kinetic studies have measured activity only on the substrates independently. Here we present characterization of enzyme kinetics for the biophysically interesting and physiologically relevant case where two substrates exhibit competitive binding to the enzyme, for both wild type and disease causing mutants of ADSL. Preliminary data suggest equivalent specific activities may be necessary to suppress severe phenotypes from expressing. Additionally, we will present results on the role of mutations on the thermodynamic stability of the enzyme. We will discuss thermodynamic analysis that gives a direct quantitative measure of the propensity of formation of folded and unfolded states of the protein, which influence the functionality of the protein and may also influence aggregation.

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