Investigating the dynamic and complex oligomeric states of aldehyde dehydrogenase 7A1

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Aldehyde dehydrogenase 7A1 (ALDH7A1) functions in lysine catabolism by catalyzing the NAD^+-dependent oxidation of α-aminoadipate semialdehyde to α-aminoadipate. Initial in-solution and *in crystallo* structural studies of ALDH7A1 suggested a static tetrameric assembly. However, more detailed analysis by analytical ultracentrifugation (AUC) revealed ALDH7A1 exists in a dimer-tetramer equilibrium with a modest dissociation constant (16 μM) (1). Recent results also suggest the oligomeric state of ALDH7A1 is dramatically influenced by a mobile C-terminus and the binding of active site ligands. These new findings have implications for understanding the molecular basis of the autosomal recessive seizure disorder pyridoxine-dependent epilepsy (PDE), which is caused by mutations in the *ALDH7A1* gene. Many PDE-linked mutations target residues in the C-terminus and oligomeric interfaces of ALDH7A1, implying that disease states may result from disruption of the self-association equilibrium. Herein we will describe an integrative biophysical and structural study utilizing SEC-MALS-SAXS, AUC, and electron microscopy to probe the oligomeric states of wild-type ALDH7A1 and several disease-linked variants. Analysis of the in-solution oligomeric behavior of a C-terminal deletion mutant lacking the last 8 residues revealed a dramatically perturbed self-association equilibrium and introduced the possibility of a trimeric assembly, which has not previously been identified in aldehyde dehydrogenases (2). In addition, a number of PDE-linked variants result in formation of potentially trimeric species in solution. Overall, studies of both laboratory and PDE-related mutations in ALDH7A1 have revealed a connection linking catalytic activity and oligomeric state. These results add to a growing body of research suggesting that disease-related mutations propagate inactive oligomers that sequester inactive enzymes.

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