The Role of Intrinsic Disorder in Human UDP-Glucose Dehydrogenase

Nicholas D. Keul, Renuka Kadirvelraj, Krishnadev Oruganty, Samuel J. Polizzi, and Zachary A. Wood

Biochemistry & Molecular Biology, University of Georgia, Athens, GA 30602, USA

It is estimated that 33% of eukaryotic proteins contain at least one intrinsically disordered (ID) segment of 30 residues or longer.[1] Many of these ID-peptides are believed to be important for enzyme function or regulation, but only a few examples have been examined experimentally.[2] Here we show that the disordered C-terminus (ID-tail) of human UDP-α-D-glucose-6-dehydrogenase (hUGDH) contributes to the allosteric regulation of the enzyme. The crystal structures of hUGDH show that the ID-tail is disordered in both the active and allosterically inhibited conformations. Despite the disordered state, the deletion of the ID-tail (**Δ**C-term hUGDH) reduces the affinity for allosteric inhibitor UDP-xylose by more than an order of magnitude. The fact that the bound allosteric inhibitor is not solvent accessible suggests that any interaction between the ID-tail and the effector involves an indirect mechanism. Given that the hexameric assembly of hUGDH is important for the allosteric response[3], we examined the effect of the ID-tail on the structure of the enzyme. The crystal structures of **Δ**C-term and full-length hUGDH reveal the same hexameric complex. However, sedimentation velocity analysis shows that the loss of the ID-tail weakens the hexamer in solution. To decouple the contribution of the hexameric structure and the ID-tail from the binding of UDP-Xyl, we used a stabilized hUGDH dimer (M11-hUGDH). The M11-hUGDH dimer binds UDP-Xylose with a greater affinity than the hexamer. As observed in the full-length enzyme, deletion of the ID-tail in the M11-hUGDH dimer reduces the affinity for allosteric effector (6.4-fold). Thus, we show that the mechanism by which the ID-tail favors allosteric inhibition is independent of its role in stabilizing the hUGDH hexamer.

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