Intrinsically disordered regions of alanine:glyoxylate aminotransferase shape its fitness and function

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Intrinsically disordered regions (IDR) play a key role in shaping the plasticity of proteins and often define their function. However, how protein evolution co-opts IDRs to impact on the population of native protein conformers and their individual fitness has remained unexplored. Alanine:glyoxylate aminotransferase (AGT) is a liver pyridoxal 5'-phosphate-dependent enzyme involved in the detoxification of glyoxylate and the cause of primary hyperoxaluria type I (PH1) when dysfunctional. In Caucasian population, AGT is present in two allelic forms, the major (AGT-Ma) and the minor (AGT-Mi) alleles, the latter increasing the susceptibility of AGT to PH1-causing mutations. By solving the crystal structure of AGT-Mi we identified three distinct regions exposed to the solvent that have a defined structure in AGT-Ma but are disordered in AGT-Mi. Molecular dynamics showed that AGT-Mi samples more flexible conformations than AGT-Ma supporting the hypothesis that IDRs originate from an enhanced plasticity of the entire structure. Characterisation of variants from a library of these three regions shed light on their effect on enzymatic activity and intrinsic stability of AGT. In addition, the analysis of the behaviour of selected hits from the library in human cells, paired with determination of the interactome of AGT-Ma and AGT-Mi, revealed the impact of IDRs on protein fitness and function at a cellular level. This work establishes that naturally occurring conformers generating by taking advantage of subtle instability of a protein can modulate its function and intracellular fitness.

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