

The Role of Protein Dynamics in Enzymatic Catalysis: Investigating the cis/trans isomerase activity of Cyclophilin A*

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Abstract

Protein dynamics or the internal motion within proteins has been previously implicated in many aspects of enzyme function such as substrate or cofactor binding, product and cofactor release, and allosteric effects. However, the connection between protein dynamics and substrate turnover has been the subject of intense ongoing research.

We have performed computational studies designed to investigate the role of protein dynamics in the detailed mechanism of peptidyl-prolyl cis/trans isomerization (PPI) reaction catalyzed by Cyclophilin A (CypA). Multiple sequence alignment of proteins with PPI activity from diverse organisms was used to generate a set of conserved residues. This set of residues was monitored during a series of molecular dynamics simulations (of human CypA), which together describe the course of reaction. Covariance analysis was performed to calculate the degree of correlation between the set of conserved residues and the residues of the peptide substrate. The results indicate that some of the conserved residues show a high degree of correlated motions. Slow conformation fluctuations of the protein were also studied with the principal component analysis. The discovered motions occur at time scales ranging from picoseconds to milliseconds and have an impact on the catalytic cycle.

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