Study of Red/ox Dynamics of Human Protein Disulfide Isomerase by Machine Learning and Network Analysis

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Abstract: The presence of a specific tetra-domain multifunctional enzyme known as the human protein disulfide isomerase (hPDI), is pivotal for regular functioning of almost all cells [1]. Thiol-disulfide interchanges in hPDI terminal domains leads to the formation of two red/ox states with different conformational preferences known as the “capped” and “uncapped” structures, respectively [2]. These redox-associated conformational dynamics are important for its substrate binding and functional activities [3]. In this study, we addressed two important issues related to the hPDI red/ox conformational dynamics i.e. (1) dynamical differentiation of red/ox-induced conformations, and (2) their effects on hormone-binding capacity of hPDI.

To investigate dynamical behavior of red/ox states, conformational ensembles were generated through molecular dynamics (MD) simulations. Then, collective domain motions were identified by the principal component analysis of MD trajectories. Machine learning classifiers were employed to extract structural features that exhibit considerable differences in dynamics of oxidation states. These features could explain distinct red/ox behavior of hPDI. To provide a comprehensive roadmap of pairwise residue non-covalent interactions in red/ox conformations, all structures were mapped into the time series of residue interaction networks and eventually compiled into a single dynamic residue interaction network (DRIN). Differential comparison of DRIN in oxidized and reduced states revealed chains of residue interactions that represent potential allosteric paths between catalytic and ligand binding sites of hPDI.

Another approach was to study the effects of red/ox-associated conformational dynamics on hormone-binding capacity of hPDI using 17 beta-estradiol (E2) as the potential interacting endogenous hormone. This was also done by ensemble docking of clustered structures of red/ox states following by the MD simulations. Analyzing of clustered binding sites indicated that both position and the affinity of E2 interaction were affected by hPDI oxidation cycle. This might have impact on regulation of hPDI red/ox functional activities within the plasma membrane and endoplasmic reticulum of cells