Molecular dynamics and normal mode analysis to understanding the mechanism of substrate-entry in prolyloligopeptides: implications for better drug design

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Abstract

This talk describes a computational study of substrate entry and product exit mechanisms of an important family of enzymes. The Prolyloligopeptidases (POPs) are enzymes that cleave peptides at Pro-X bonds and are biomedically important since they are implicated in neurodegenerative diseases. A detailed mechanism of substrate entry would be vital for the development of drugs. Following homology modeling of the human PoP from porcine PoP structure, we first demonstrated that the drug binding affinities of the two proteins could be different. An “open” structure of the substrate-unbound form of eukaryotic POPs was lacking and we have addressed this using a combination of homology modeling, normal mode analysis (NMA) and long-length essential dynamics of protein to study the possible mode of substrate entry. Our study shows that eukaryotic POPs are also likely to go through large interdomain movements and go through an “open” conformation, much like the prokaryotic POPs. Further, our NMA and close to 750 ns of simulations show that interdomain twisting motion occurs and this is facilitated by an up-down motion of the unique N-terminal region in POPs. We propose an overall model for the mechanism of substrate entry for POPs.

References: