Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Seminar

Effect of the L99A Cavity Creating Mutant on the Backbone Flexibility of T4 Lysozyme

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Mutating leucine 99 to alanine in the C-terminal domain of lysozyme from T4 Phage (L99A T4L) creates a solvent inaccessible cavity inside the protein core that is capable of binding small hydrophobic ligands like benzene[1]. Ligand binding also stabilises L99A T4L compared to its unbound form. Earlier studies suggest that benzene binds to the cavity with remarkably fast rate (k_{on} ~10^6 $M^{-1}S^{-1}$) despite being buried inside the protein core[2]. We studied how benzene reaches this solvent inaccessible cavity using molecular dynamics (MD) simulations combined with NMR experiments. The MD simulations showed that benzene reaches the cavity through three distinct pathways that involves subtle motion of helices in the C-terminal domain of the protein that creates tunnels from the surface to the buried cavity. The simulation also suggest that the helix-helix motion is energetically favorable in L99A T4L compared to its wild type analog (WT* T4L). We estimated the backbone order parameters (S^2) in WT* T4L and L99A T4L from backbone chemical shifts. S^2 reports on the dynamics of protein backbone occurring on the pico-nanosecond (ps-ns) time scale. Our results show that the mutation does not have a significant effect on the ps-ns dynamics of the protein backbone despite the increase in flexibility implicated in the rapid binding.

References:

1. Eriksson AE, Basse WA, Zhang XJ, Heinz DW, Blaber M, Baldwin EP, Matthews BW, Science 1992, 255, 178-183.
2. Feher VA, Baldwin EP, Dahlquist FW, Nature Structural Biology 1996, 3, 516-521.

Monday, Sep 19th 2022

11:00 AM (Tea/Coffee at 10:45 AM)

Auditorium, TIFR-H