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

Webinar

From Biophysics to Fitness: Bridging Scales in Biology to Understand Genotype-Phenotype Relationship

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A mechanistic understanding of effect of mutations on fitness (genotype-phenotype relationship, GPR) is a central challenge in modern biology. We address this problem bottom up by probing effect of mutations on molecular properties of macromolecules as well as through multiscale analyses that span several levels of biological organization.

In this talk, I will discuss our recent work that uses metabolomics analyses to demonstrate a precise mechanistic understanding of how metabolic perturbations arising out of mutations affect phenotype. We find that *E.coli* strains that carry destabilizing mutations in Dihydrofolate Reductase (DHFR) show a highly filamentous morphology. Partial loss of DHFR activity in these mutants causes SOS response indicative of DNA damage and cell filamentation. This phenotype is triggered by an imbalance in deoxy nucleotide levels, most prominently a disproportionate drop in the intracellular dTTP. However, dTTP levels could not be explained by drop in dTMP based on the Michaelis-Menten like in vitro activity curve of Thymidylate Kinase (Tmk), an enzyme downstream of DHFR that phosphorylates dTMP to dTDP. Instead, we show that a highly cooperative (Hill coefficient 2.5) in vivo activity of Tmk is the cause of suboptimal dTTP levels. dTMP supplementation in the media rescues filamentation and restores in vivo Tmk kinetics to almost perfect Michaelis-Menten. The cooperative enzyme activity is best explained by the fractal nature of Tmk activity in vivo due to diffusion-limitation of substrate dTMP, possibly due to substrate channelling and metabolon formation. Overall, this study highlights the important role of cellular environment in sculpting enzyme kinetics. It also demonstrates the use of a systems level property of the cell – metabolome – as a stepping-stone to illustrate precise biophysical and biochemical mechanisms to bridge the multi-scale genotype-phenotype relationship.

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5:00 PM