Cellular Energy Regulation from a Single-Molecule Protein Dynamics Perspective

Haw Yang

Department of Chemistry, Princeton University, Princeton, NJ, 08554, USA

MAGNESIUM ion (Mg^{2+}) is required for various biochemical functions and is tightly regulated in cells. Due to its essential roles in phosphoryl transfer and ATP hydrolysis, it has been proposed that Mg^{2+} could be important in energy homeostasis, mediated through the adenyate kinase (AK) enzyme during transient response. We provide enzymatic kinetics evidence to support this model. We found that the ATP-consuming reaction of AK is accelerated by binding to an additional Mg^{2+}. Our findings thus frame a hypothesis that AK serves as a coupling enzyme between the Mg^{2+} regulatory network and bioenergy homeostasis where the Mg^{2+}-activated mechanism helps to cope with transient increase in Mg^{2+} concentration.

These results lead to the question as to how, on the molecular level, AK reactivity depends on the presence of Mg^{2+}. We hypothesize that conformational dynamics play an integral role in the overall reactivity during an enzymatic cycle. Specifically, we ask the following questions: What is the number and range of conformational states accessible to enzymes during their catalytic cycle? How does the enzyme's conformation respond to interaction with substrates? At which stage along an enzymatic cycle do these changes occur? To investigate these issues, we apply high-resolution single-molecule spectroscopy to unravel the mechanistic roles of protein conformational dynamics using adenylate kinase from *Escherichia coli* as model. Our results allow us to delineate the enzymatic reaction cycle on an experimentally measured potential of mean force whereupon such concepts as dynamically induced fit and conformational gating are illustrated.