Contribution ID: **40** Type: **not specified**

Short Talk 8, Yong Wang - Integrative Ensemble Modeling of a Large Membrane Protein Complex Using Diverse and Ambiguous Information

Thursday 10 October 2019 16:10 (20 minutes)

Mitochondria contain approximately 1200 different proteins, 99% of which are synthesized on cytosolic ribosomes and need to be delivered into the right destination through the intermembrane space by transport machineries, such as the TIM chaperone. Currently, the mechanistic and structural details of how the TIM chaperone binds to these mitochondrial proteins remain elusive. To gain structural insight into the binding and chaperone mechanisms, we focused on the complex of the TIM9/10 chaperone and the mitochondrial GDP/GTP carrier membrane protein (Ggc1). Such complexes are difficult to study because they consist of a transiently formed, dynamic complex between two folded proteins and a membrane protein that should be solubilized and bound by the chaperone. X-ray crystallography has revealed the core structure of the free chaperone protein, but because of the dynamic nature and large size (~1400 amino acids) of the complex its structural features have remained elusive. Using an integrative approach that combines biochemical assays, NMR spectroscopy and SAXS it was, however, able to obtain detailed but ambiguous information on the structures of the complex. In particular, the experiments showed that the complex consists of two well-structured (TIM9)3/(TIM10)3 hexamers bound to a mostly disordered Ggc1. In this work, we developed a protocol to integrate such heterogeneous experimental data with a coarse-grained molecular model to provide a description of the conformational ensemble of the TIM9/10-Ggc1 complex. In particular, we used a hybrid structure-based model (to describe the intra-molecular interactions within the folded chaperone), an NMR-derived contact potential for chaperone-client interactions and a knowledge-based potential (to describe the inter-molecular interactions between the chaperones and chaperone-client interactions). We used molecular dynamics (MD) simulations to sample the conformational landscape of the complex, and the resulting coarse-grained conformational ensemble was subsequently converted into all-atom resolution and refined using a Bayesian/Maximum Entropy re-weighting approach using the SAXS data. This allows us to generate a weighted ensemble in agreement with experimental measurement. Such integrative structural modeling method is useful to generate a structural ensemble of large and dynamic proteins in a both efficient and reliable way.

Reference:
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Session Classification: Keynotes and Short talks 6