MS11-O5

Structural basis for RpoS regulation via ClpXP adaptor/anti-adaptor pairs

Alexandra Deaconescu[1], Victoria Dorich[1], Margaret Suhanovsky[2], Arti Tripathi[3], Song Tong[3], Christiane Brugger[1], Joel Hoskins[3], Sue Wickner[2], Susan Gottesman[3]

1. Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, United States of America
2. Department of Molecular Biology, Cell Biology and Biochemistry, Providence, United States of America
3. Laboratory of Molecular Biology, National Cancer Institute, Bethesda, United States of America

email: alexandra_deaconescu@brown.edu

The promoter dissociable subunit RpoS is widely recognized as the master regulator of the bacterial stress response. Its intracellular levels are not steady, but fluctuate in response to nutrient starvation or other environmental stress signals such that during the logarithmic phase, RpoS is almost undetectable, while in stationary phase, it rapidly accumulates to enable transcription reprogramming via control of a large regulon. This process is largely controlled at the level of RpoS proteolysis by the ClpXP machinery, which readily occurs under active growth, and is inhibited upon stress. Here we provide mechanistic and structural insights into how RpoS delivery to the ClpXP machine is inhibited by small factors collectively called anti-adaptors. Anti-adaptors are induced by specific stress signals and bind to RssB, a ClpXP adaptor of exquisite specificity that is required for RpoS loading onto ClpXP and represents the limiting factor in this process. Our data suggest that anti-adaptors may utilize modes of RssB recognition that rely heavily of RssB plasticity.

Keywords: RpoS, ClpXP, RssB

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MS12-O1

Using evolutionary couplings to predict contacts and build structures

Kelly Brock[1], Chris Sander[2], Debora Marks[1]

1. Department of Systems Biology, Harvard Medical School, Boston, MA, United States of America
2. cBio Center, Dana-Farber Cancer Institute + Harvard Medical School, Boston, MA, United States of America

email: kpgbrock@gmail.com

Recent advances in crystallography have helped deliver unparalleled biological insight; however, the rate at which experimental structures can be solved still lags behind the need to better understand many biomolecules. Our research aims to significantly **accelerate** the accumulation of structural knowledge through computational means, including collaborating with experimental labs to help solve and refine models of protein monomers and complexes.

To help bridge the gap between protein sequence and 3D structure, our lab uses a protein's evolutionary history to predict which residues are most likely to physically interact. Identifying potential interacting pairs, or **evolutionary couplings (ECs)**, can be achieved by finding related sequences and applying a global probability model to search for covariation patterns consistent with interacting residues. We have shown that ECs can be sufficient to predict the tertiary fold of a protein [1,2], and thousands of pre-computed models along with our web server can be found at **EVcouplings.org.**

We recently helped solve the structure of the 359-residue transmembrane protein RodA by generating a de novo folded model that was sufficient for molecular replacement, and we predicted how it forms a complex with its binding partner PBP2 [3]. We can provide models for unknown component structures in 3D complex determination, along with predictions about protein-protein contacts. Here, we present the potential for ECs to help build and refine models in conjunction with crystallography data.

References:

[1]. Marks, DS et al. Protein 3D Structure Computed from Evolutionary Sequence Variation. PLoS One 2011.
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[3]. Sjodt, M et al. Structure of the peptidoglycan polymerase RodA resolved by evolutionary coupling analysis. Nature 2018.

Keywords: molecular replacement, contact prediction