Design of Protein Functions Using Computational and Experimental Approaches

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Our research is to design a variety of protein functions using computational and experimental approaches. We try to (1) design enzymes from scratch and reveal the origin of the enzymatic activity, (2) control concerted functions by rationally engineering protein complexes and understand their mechanisms and (3) uncover roles of protein complexes in cells and control cellar functions by creating several customized proteins or protein complexes.

1. De Novo Design of ATPase

ATP hydrolysis plays pivotal roles in various proteins, including molecular motors and kinases. To elucidate the minimal structural requirements for ATP binding and hydrolysis, we computationally designed an ATPase from scratch, focusing the P-loop motif, a conserved phosphate-binding loop found in many naturally occurring ATPase.

Using computational design methods, we systematically explored an optimal topology that harbor the P-loop motif and facilitate binding to the adenine ring of ATP. Main-chain structures corresponding to the identified topology were generated, and amino acid sequences were designed to stabilize the main-chain structures and optimize ATP binding.

Biochemical assays for the designed proteins verified that one design was soluble, monomeric in solution, and exhibited ATP hydrolysis activity. Moreover, its crystal structure closely matched our design model and contained a P-loop motif with the typical features. We successfully demonstrated how to design a P-loop containing ATPase from scratch.

Reference

1) T. Kosugi, M. Tanabe and N. Koga, *Protein Sci.* **34**, e70132 (2025).

Award

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