MOLECULAR ENGINEERING

2D protein lattices by design

Researchers design programmable two-dimensional (2D) protein lattices that may find broad applications in diverse fields.

Researchers in David Baker's laboratory at the University of Washington have long been applying a general computational approach known as rational design to create new proteins. They have successfully constructed scores of designer proteins with novel folds and novel functions, even enzymatic activities not found in nature.

In his latest venture, Baker joined forces with Tamir Gonen, a molecular electron microscopist at Janelia Research Campus, to attempt a difficult design challenge: creating an ordered, symmetrical 2D protein lattice from scratch. Although a few examples of 2D protein lattices—consisting of individual subunits arranged in a regular array held together by extensive noncovalent interactions—are found in nature, it has been difficult to design them successfully in a lab.

The researchers first evaluated the possible ways in which protein building blocks, being 3D objects, could come together to form a symmetric 2D array using only two unique noncovalent interfaces. Finding six suitable ways, they then applied the Rosetta protein modeling software to dock building blocks in a symmetrical array while at the same time optimizing their shape complementarity. Upon identifying the building blocks with the largest number of noncovalently interacting residues, they used Rosetta to further design optimal protein sequences that would ensure that the building-block interfaces were well packed and low energy.

The researchers next obtained synthetic genes for their 62 best designs and expressed them in *Escherichia coli*. 43 of the 62 lattices expressed successfully; however, just three formed planar lattice arrays in *E. coli* as observed by electron microscopy. Choosing one of the designs to examine in detail with cryo-electron microscopy and electron diffraction, the researchers obtained structural data at 4-angstrom resolution. This showed that the lattice was highly ordered and that its structure was consistent with the designed model.

The researchers write that "The ability to precisely design 2D arrays at the near atomic level should enable new approaches in structural biology, … new sensing modalities with the coupling of analytic binding domains to the arrays, and the organization of enzyme networks and light-harvesting chromophores in two dimensions."

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RESEARCH PAPERS

Gonen, S. *et al.* Design of ordered two-dimensional arrays mediated by noncovalent protein-protein interfaces. *Science* **348**, 1365–1368 (2015).