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Coiled coils unspring protein origami

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Abstract

Self-assembling sequences of protein coiled coils create polyhedral nanostructures for advanced applications in biomedicine, chemistry and materials science.

As a proponent of ‘functional design’, the minimalist architect Ludwig Mies van der Rohe believed that “Architecture starts when you carefully put two bricks together.” In this issue, Ljubetič *et al.*[1] use α-helices as bricks to achieve architectural integrity with simplicity in protein design. By placing α-helices along an amino acid chain in such a way that they form coiled coils with cognate α-helices far apart in the sequence, the authors create hollow triangular pyramids, square pyramids, and triangular prisms that match predetermined shapes. In contrast to the group’s earlier report on this approach[2], the polyhedra self-assemble *in vivo* and *in vitro*. This robust design platform, built on a sturdy protein secondary structure, opens many opportunities to couple protein function to form.

Helical forms compel comparisons between DNA and protein coiled coils. The coiled-coil structure was first deduced in 1952 by Francis Crick from fiber diffraction data on α-keratin[3]. In the 1980s, the finding that coiled-coil α-helices contain a seven-amino-acid repeat pattern led to the prediction of coiled coils far longer than any protein helices yet observed[4]. Indeed, the longest naturally occurring helices are part of coiled coils.

In human cells, coiled coils can hold DNA ends to keep strand breaks from becoming chromosome breaks[5]. In bacteria, they form the micron-long filaments that enable adherence and movement on host cells. Such cases exemplify common functions of coiled coils: their length enables action across long distances, and they have a great capacity to hold a net charge to form interfaces with proteins and nucleic acids.

The rules of assembly for coiled coils are analogous to those of the DNA double helix, but more complex. These rules have been intuitively deduced, and coiled-coil formation can be predicted. An early *de novo* design predicted a structure to within 0.2 Å root mean square deviation to its crystal structure[6]. The structural and chemical features of coiled coils make them ubiquitous in cells—and ideal building blocks for designed nanostructures.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Ljubetič *et al.*[1] were inspired by the similarities between DNA and coiled coils and by recent advances in DNA origami, in which strands of DNA are folded via Watson–Crick base pairing into a large variety of 2D and 3D structures[7]. The essence of origami is to make complex shapes by folding a single continuous entity. In the authors' new system, called 'coiled-coil protein origami', the continuous entity is a single polypeptide chain containing multiple α-helical and linker regions (Fig. 1). After folding, the α-helices contribute to a unique coiled coil along an edge of the polyhedral form.

In a previous study from the same laboratory, this approach was used to construct a triangular pyramid, but the structure required refolding owing to insolubility of unfolded intermediates and the existence of trapped intermediate states[2]. Supercharging, introduced in the present report[1], is the key to overcoming folding bottlenecks. The result is a computational platform for coiled-coil origami design that takes the desired geometry as input and outputs several complete sequences composed of unique coiled-coil-forming segments, along with a three-dimensional model of the design. The authors experimentally validate three prototypic models (triangular pyramids, square pyramids, and triangular prisms), but the outlined procedure appears applicable to hollow polyhedra of any shape, provided that the number of edges is smaller than the number of unique coiled-coil segments. The authors observed proper folding not only *in vitro* but also in cells and mice.

Central to the experimental validation of the models is small-angle X-ray scattering (SAXS), which has become a technique of choice for protein design[8,9]. SAXS measures molecules in solution and can be conducted and analyzed at high throughput[10]. Thus, not only can many sequences be tested, but the conditions that favor the design can be identified. Furthermore, many designed proteins, including those made by coiled-coil protein origami, are flexible and therefore unlikely to be amenable to techniques that require strict conformational homogeneity, such as X-ray crystallography. SAXS has been similarly applied to validate several notable protein designs from other groups.

Most macromolecular design efforts to date resemble Mies van der Rohe's 'skin and bones' architectural style. DNA origami is usually composed of DNA alone, without added functional moieties, and the coiled-coil protein origami demonstrated by Ljubetič *et al.*[1] is similarly minimalist. But as amino acids have chemically diverse side chains, many opportunities exist to add functionality and put muscle on the bones. For example, enzyme active-site motifs could be incorporated at the vertices of the polyhedra. As with DNA origami, potential biomedical applications include drug delivery and vaccination. But the utility of programmable nanostructures has only begun to be explored. In applied chemistry, one can envision the design of self-assembling catalytic arrays; catalytic activities could even be coupled to action over distance, as cooperative allosteric linkages are a common feature of coiled-coil function in cells. In material science, nanostructures could be used in bottom-up printing strategies. Thus, coiled-coil protein origami opens the door to a functional design architecture that incorporates the many activities that only proteins have evolved to possess.

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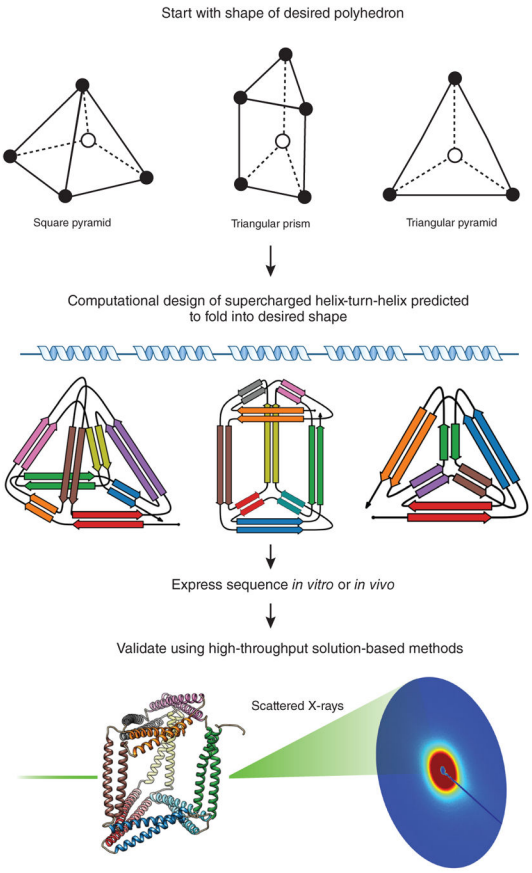

Figure 1.

Computational and experimental framework for coiled-coil protein origami. Polypeptides coding for helix-turn-helix sequences form designed polyhedra whose edges are coiled coils.