Designing with nanoscale building blocks: engineering self-assembling protein superstructures for applications in vaccines, drug delivery and biochemical production

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1. Abstract

Self-assembling proteins make up precisely ordered nanostructures such as filaments and capsules, each of which is promising for applications in medicine and materials. For example, a nanoscale protein capsule could serve as a delivery vehicle for cellular and gene therapy applications or as a vaccine scaffold. However, such structures must be tunable for each application, and to date, the ability to predict how alterations to the protein sequence will impact self-assembly and other structural properties remains a significant challenge. To address this challenge, we combined comprehensive mutagenesis with high-throughput sequencing to fully characterize the assembly-competency of several self-assembling proteins, including those from a virus-like particle, a bacterial microcompartment, and a secretion system. The resulting high-resolution fitness landscapes challenge several conventional protein design assumptions on the composition of linkers, mutability of pore-lining residues, and more. We then used the same approach but with other functional screens to design each system for enhanced performance in applications. For example, the virus-like particle was engineered for controlled acid stability and separately for increased stability to bioconjugation reactions, while the microcompartment particles were adapted to make altered geometries useful as materials. With this talk, I will provide examples of how our sequencing-based approach is useful as a tool for uncovering the fundamental rules of self-assembly as well as for engineering new function into self-assembling systems.