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Thesis outline

In nature, some proteins self-assemble into shell-like structures which are highly stable systems for encapsulation and surface modifications to optimize functions. Protein cages can be artificially designed to encapsulate enzymes and have multiple applications. However, the current functionalization of protein cages often requires external enzymes, co-factors, or metals, which may result in lower-than-expected activity and can introduce undesirable side effects, toxicity, reduced stability, and low biocompatibility. In this doctoral thesis, I utilize ferritin, a well-studied protein cage, to do structural and functional design. On the two-fold interface, previously research designed different residue clusters with various positions and can immobilize metal ions. This approach allows for creating desired structures and functionalities through residue clusters without using any exogenous components. The cage structure can facilitate the reaction in a confinement environment. My research focuses on structural design, analysis, and activity characterization, to establish and understand the relationship between structure and function. By residue substitution, I seek to overcome the challenges of using external agents, ultimately creating a more efficient and predictable protein cage system for various applications.

In Chapter 2, I focused on designing a ferritin cage with peroxidase-like activity through histidine substitution. I used the two-fold symmetric interface of ferritin as a scaffold to design various histidine clusters. This part manuscript is under preparation.

Protein crystals are solid assemblies consisting of protein molecules in a regular arrangement. Through the engineering of amino acid residues, exogenous compounds such as dye molecules and metal complexes can be immobilized to develop hybrid solid materials. Besides small molecules, the immobilization of protein into in-cell crystals is a remarkable method of synthesizing solid-state materials. In Chapter 3, based on the results from Chapter 2, I utilized the mutants developed in the previous chapter and fused ferritin with Crystalline Inclusion Protein A (CipA). This fusion protein enabled ferritin to form protein crystals within cells spontaneously. The resulting ferritin-fused crystals exhibited peroxidase-like activity, with enhanced catalytic activity observed in the mutation. This study presents a straightforward approach to developing functional solid materials, showcasing the potential of using protein crystals for catalytic applications and further expanding the versatility of protein cages in material science.

In Chapter 4, I investigated whether isolated ferritin crystals exhibit any unique structural features. Through X-ray structural analysis, I discovered a unique water network structure made up of five fused pentagonal water rings, which was called semi-clathrate. This semi-clathrate structure is typically observed in antifreeze proteins, where it supports the inhibition of ice crystal growth. I further explored the semi-clathrate structure in ferritin under varying temperatures and designed several mutants to study its formation mechanism. I found that both temperature and alanine residues play important roles in the formation of the semi-clathrate structure. The formation of semi-clathrate is influenced by temperature, and this process is reversible.

In Chapter 5, since ferritin remained stable even after substituting multiple amino acids with histidine at the two-fold symmetric interface, I continued to use the two-fold symmetric interface as a scaffold construct semi-clathrate. This part manuscript is under

preparation.