Significant findings about protein architecture may aid in drug design, generation of nanomaterials

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Researchers in Singapore are reporting this week that they have gleaned key insights into the architecture of a protein that controls iron levels in almost all organisms. Their study culminated in one of the first successful attempts to take apart a complex biological nanostructure and isolate the rules that govern its natural formation.

The Nanyang Technological University team's work on the protein ferritin, the results of which appear in this week's issue of the Journal of Biological Chemistry, is expected to have significant ramifications on the fields of drug design and nanomaterials.

"Engineering the structure of a protein is one of the ultimate dreams of structural biologists," wrote one of the journal's peer reviewers, "and approaching that dream is greatly enabled through studies aimed at finding out what governs the nanoarchitecture of the protein."

Brendan P. Orner, the assistant professor who oversaw the team's work, described the protein ferritin as a potential model for explaining complicated protein structure in general.

Across the biological kingdoms, ferritin regulates the distribution of iron, which is necessary for a number of cellular functions but also forms reactive ions that can be lethal to cells. Shaped like a spherical nanocage, ferritin is made up of 24 proteins, and it sequesters the reactive iron ions in its hollow interior. In humans, ferritin prevents iron deficiency and overload.

"The rules that govern self-assembling nanosystems, like the ferritin model, are poorly understood," Orner explained. "We systematically analyzed the interactions between the 24 ferritin units that make up the nanocage and identified the hot spots that are crucial to the cage's formation."

Their goal was to discover which amino acids are responsible for assembling the cage, and they found that it is possible to both disassemble ferritin by removing single side chains of amino acids and, surprisingly, to stabilize the structure by removing other side chains.

Understanding the assembly of the nanocage could open the door to drug design that will disrupt the structure and function of defective proteins that cause or contribute to disease. It also may aid in the creation of biological nanostructures in which scientists can grow special particles and materials with a variety of properties and applications.

"Cell biology provides many structures that are on the nanoscale and have amazing complexity and symmetry," Orner said. "The problem is that many of these structures are, like ferritin, self-assembled proteins, and, if we are going to use them for nanomaterials applications, we need to understand the fundamentals that make them form this way naturally."

Orner and his team members are particularly interested in growing nanoparticles of precise dimensions inside ferritin shells. Already, they have developed a new method to grow gold nanoparticles in them.

"Slight deviations in size or shape can radically change nanoparticles' properties, particularly in the case of metals and semiconductors," Orner said. "Our ferritin proteins are hollow, so, when we grow mineral or metal clusters inside them, the growth stops when the nanoparticles reach the limits of the protein shell."

By studying the rules that control the folding and assembly of such a protein in nature, Orner said, the investigators hope to be able to manipulate them one day to create new proteins with novel sizes and shapes and, therefore, generate nanoparticles of novel sizes and shapes inside them.

"Those nanoparticles could be used for in-vitro assays to do high-throughput drug screening of some protein-protein interactions involved in virus infection and cancer, for example," he said.

Orner's team included doctoral students Yu Zhang and Rongli Fan, undergraduate students Siti Raudah, Huihian Teo and Gwenda Teo, and scholar Xioming Sun. Their research was funded by the Singapore Ministry of Education and Nanyang Technological University.

Their resulting article has been named a "Paper of the Week" by the *Journal of Biological Chemistry*, putting it in the top 1 percent of papers reviewed by the editorial board in terms of significance and overall importance.

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