Phoenix effect—resurrected proteins double their natural activity

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An artist's representation of a Phoenix. Credit: ITMO University

Proteins play a large role in sustaining life functions. These molecules ensure that vital reactions, such as DNA replication or metabolism catalysis, are carried out within cells. Protein denaturation is accompanied by the unfolding of the native three-dimensional structure

of the protein and hence the loss of its activity. By reassembling this polymer tangle, it is possible to renature the protein and restore its activity, but this procedure requires much effort.

Denatured proteins often pile up to form toxic aggregates, which is the underlying reason for many illnesses such as Alzheimer's, Parkinson's and Huntington's. Therefore, the investigation of denaturation and renaturation mechanisms is critical.

In a new study, David Avnir, professor at the Hebrew University in Jerusalem, and Vladimir Vinogradov, head of the International Laboratory of Solution Chemistry of Advanced Materials and Technologies at ITMO University, found that reviving proteins is not only possible, but can be carried out with an improvement over their original activity. The researchers describe a new technique of protein renaturation based on combining thermally denatured proteins (carbonic anhydrase) with a colloid solution of inorganic aluminum oxide nanoparticles.

As the solution becomes a gel, the nanoparticles bind together, exerting mechanical pressure on the protein molecules. As a result, each molecule becomes entrapped in its own individual porous shell, which prevents the malign process of protein aggregation and eventually restores the original spatial structure. By comparing the protein activity levels before denaturation and after renaturation, the chemists discovered that the resurrected proteins were 180 percent more active than their native predecessors.

"Every protein molecule has its active center, which allows the molecule to interact with the environment. The active center, however, constitutes only 5 to10 percent of the molecule surface," explains Vladimir Vinogradov. "During renaturation, we deal with a long, unfolded molecule containing an active center and several extending tails. The

active center and nanoparticles have similar charges and will repel, while the tails have an opposite charge and will gravitate toward the nanoparticles. In the end, when a shell forms around the molecule, the active center will be as far away from the wall of the shell as possible, thus increasing the protein's chances to interact with the substrate."

Researchers say that this technique only works with unfolded denatured proteins. The orientation of native proteins within the shell cannot be controlled in the same way, because the active center can find itself anywhere, including facing the wall, excluding the possibility of interacting with the substrate.

As professor David Avnir explains, one possible application of the discovery is optimizing the fabrication of drugs based on active proteins:

"Some of the most effective drugs are based on active proteins that are harvested from cell cultures. However, among all proteins grown in such a way, only 20 percent are native and suitable for use, while the remaining 80 percent are the so-called inclusion bodies—that is, non-functioning denatured proteins. Obviously, knowing how to convert denatured proteins to their native state, with increased activity levels, would allow pharmaceutical companies to lower the price of many drugs, making them more affordable."

Provided by ITMO University