Chaperonins prompt proper protein folding -- but how?

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In proper society of yesterday, the chaperone insured that couples maintained proper courting rituals. In biology, a group of proteins called chaperonins makes sure that proteins are folded properly to carry out their assigned roles in the cells.

In a new study in archaea (single-celled organisms without nuclei to enclose their genetic information), a consortium of researchers from Baylor College of Medicine and Stanford University in California discovered how the Group II chaperonins close and open folding chambers to initate the folding event and to release the functional protein to the cell. A report of their work appears in the current issue of the journal *Nature*.

Archaea is one of three major divisions in the classification of living organisms. The other two are bacteria and eukaryotes. Archaea lack a nucleus but have other characteristics that are similar to those of eukaryotes, which include human beings.

"The important thing about the chaperonin molecule is that it is key to folding proteins in the cell - key proteins such as actin, tubulin and tumor suppressors," said Dr. Wah Chiu, professor of biochemistry and molecular biology at BCM and a senior author of the report.

"Previously, people had studied chaperonins in the bacteria Escherichia coli," said Chiu, also director of the National Center for Macromolecular Imaging and of the Nanomedicine Development Center at BCM. "We

wanted to look at how chaperonins operated in a new class of organisms, and we chose the archaea."

It turned out that the archaea have a different type of chaperonin dubbed Group II. The structure of this kind of chaperonin is more similar to that of mammals. In essence, both types of chaperonin act as molecular machines, assisting proper protein within the cell. To the surprise of Chiu and his colleagues, the Group II chaperonin worked differently from Group I chaperonins previously studied in E. coli.

"It turns out that this chaperonin - that we call a molecular nanomachine - requires ATP (adenosine triphosphate or the major energy currency in cells) to close its chamber," he said.

The group II chaperonins that oversee proper protein folding in this organism have an upper and lower chamber and a built-in lid. ATP adds water to the chaperonin at a critical point. When the water is added, a process called hydrolysis takes place. Without ATP, the chamber is open. When ATP is added, the chamber closes.

"The take home message in this is how the chaperonin opens and closes," said Chiu. The way in which these chaperonins complete a large mechanical motion critical for completing a protein-folding event is different from that of others that have been studied.

Equally important is the tool he and his Stanford colleagues developed to see the complicated structure and dynamic motion of the chaperonin. Combining cryo-electronmicroscopy with intricate computer modeling, they were able to "see" the closed conformation of the single chaperonin particle at a resolution of 4.3 angstroms. (An angstrom is one hundred-millionth of a centimeter. A sheet of paper is approximately 1 million angstroms thick.) The model of the open conformation was resolved down to 8 angstroms.

The models of the open and closed structures reveal how changes in their structure triggered by ATP alter the contacts within the adjacent protein molecules within and across the two chambers, causing a rocking motion that closes the lid of the two chambers of the chaperonin.

"The technique is important in allowing us to see how this nanomachine works," said Chiu. He anticipates that future work with chaperonins in other organisms will reveal even more important structural details.

Provided by Baylor College of Medicine