Common 'chaperone' protein found to work in surprising way

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In the constantly morphing field of protein structure, scientists at The Scripps Research Institute offer yet another surprise: a common "chaperone" protein in cells thought to help other proteins fold has been shown instead to loosen them.

The study was published in the April 3 issue of *Nature Structural & Molecular Biology*.

The research offers the first structural insights into the shape of a "client" protein in the presence of a helper or "chaperone" protein. Specifically, the study examined the client protein p53 tumor suppressor and its interactions with chaperone heat shock protein 90 (Hsp90).

"It was a real surprise to find that, when bound to Hsp90, p53 is loosened and becomes less ordered, forming a molten globule-like state," said the study's lead investigator, molecular biologist Professor H. Jane Dyson. "This contradicts what everyone thought of as the function of chaperone proteins—to help other proteins fold into a well-defined three-dimensional structure."

Appreciating Versatility

The findings add to scientists' new understanding of proteins, now thought not only to constantly change shape to perform different functions, but also to be active when unfolded.

It was once thought that proteins could be active only if they were neatly folded into a compact shape and that this structure defined its function. Then Scripps Research investigators Dyson and Professor Peter Wright, as well as others, discovered that unfolded "disordered" proteins (also known as "intrinsically unstructured proteins") could also be active.

One way these intrinsically disordered proteins act is by folding when they bind to other molecules and performing a function such as potentiating cellular signaling or turning on the transcription of a gene.

The disordered protein might then dissociate from this partner, unfold, and perhaps bind to a different molecule in a new shape. Thus, these proteins can constantly move between unstructured and ordered states, interacting with many different partners as part of the "proteostasis." of the cell.

"We are realizing that proteins are a lot more versatile than we understood in the past," said Dyson.

Breaking New Ground

In the new *Nature Structural & Molecular Biology* study, the team set out to better understand the structural biology of the Hsp90/p53 complex.

Both Hsp90 and p53 are crucial to cell functioning. About one percent of proteins in a typical cell are Hsp90 chaperone molecules, and they are known to perform a number of functions, including acting as "holding" proteins for hormone receptors. The tumor suppressor p53 is a crucial cell cycle regulator; in fact, most mutations seen in cancers occur in the DNA-binding domain of p53, which is also the site of its interaction with Hsp90.

"A lot of researchers have studied the interactions of Hsp90 and its

client proteins," said Dyson. "None of these studies was able to pinpoint either what the client protein looked like in the complex or what part of Hsp90 was contacting the client."

In the new study, the team used protein nuclear magnetic resonance (NMR) spectroscopy; Scripps Research has some of the world's most powerful NMR spectrometers. Still, the research took several years to complete, given the complicated nature of the proteins, their large size, and their weak interactions.

The data ultimately showed Hsp90 acted to loosen up, or unfold, p53.

The authors suggest the interactions of Hsp90 with its client proteins are tuned to tasks as needed within a cell. "Our study demonstrates that the interaction is surprisingly non-specific," said Dyson, "and that rather than making a distinct complex, the Hsp90 causes a change in the overall structure of the client."

Hsp90 could perform other, as-of-yet-unknown functions, she added. "This is just the beginning of understanding how these important, and very common, chaperone proteins are functioning."

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