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Scientists 'watch' as individual alpha-synuclein proteins change shape

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In an Early Edition publication of The *Proceedings of the National Academy of Sciences* (*PNAS*) this week, the researchers demonstrate the "alpha-synuclein dance" - the switching back and forth of the protein between a bent helix and an extended helix as the surface that it is binding to changes.

Such shape shifting has rarely been so directly observed in proteins like alpha-synuclein, which are known to be unfolded in isolation, says the study's senior investigator Ashok Deniz, an associate professor at The Scripps Research Institute.

"We are intrigued to see such complex behavior," he says. "It is interesting that with just a single binding partner, the protein can undergo so many dramatic shape transitions, and that the whole process is reversible."

In the past, scientists believed that proteins, as directed by their genes, fold themselves into defined three-dimensional structures that dictate their function. But more recently, a class of proteins known as "intrinsically disordered proteins" have been identified, which are functional, despite the fact that they are often unfolded.

Alpha-synuclein is such a protein. Mutations in the gene that produces alpha-synuclein have been linked to early-onset Parkinson's disease, and in sporadic, common Parkinson's disease, the protein can accumulate into so-called Lewy bodies inside nerve cells. The protein is also found

in the amyloid plaques in Alzheimer's disease, and in other forms of neurological disease.

To learn more about alpha-synuclein, the Scripps Research team decided to study the shape of single proteins. To do this, they used a technique they helped develop, which is known as single-molecule fluorescence resonance energy transfer (FRET), to look at how the protein folds when it binds to different molecules. This technique, which Deniz calls a "molecular ruler," measures light emitted from fluorescent dyes that are attached to amino acids in the protein. The measured light provides information about molecular distances, hence revealing the protein's shape. By observing shapes of individual proteins rather than averaging data over a large number of them, the team was able to better map and resolve shape complexity in the system.

To coax the protein to change shapes, the researchers increased the concentration of a soapy solution that mimics the lipids found in different nerve cell membranes in the brain. Alpha-synuclein is known to bind to membranes on nerve cells, and lipids are a large component of those membranes.

At a low concentration, the "lipid" molecules remained separate but at higher concentration, small and then larger blobs of molecules form. The shape of the alpha-synuclein kept pace - the extended helix could latch onto lipid-mimics as monomers or in a large cylinder-shaped blob, whereas the bent helix wrapped itself around smaller lipid-mimic balls or could create formations with lipid-mimic monomers.

"Others have found the protein to be in a bent helix or in an extended helix, but what we are showing here directly is that the shape can actively change," Deniz says. "It starts off in an unfolded state, and as we increase the concentration of the lipid mimics, the protein reacts to what is in effect a different binding partner, even though it is the same small

molecule at different concentrations. It switches back and forth into different states.

"This is perhaps the most complex protein folding-binding system that has been studied to date using single-molecule FRET," he says.

This ability of alpha-synuclein to be switched into alternative shapes could play a significant role in regulating formation of disease-related aggregates, as well as enabling its function. Hence, one next step for the research team is to figure out which form of alpha-synuclein may accelerate formation of the types of protein aggregates found in Alzheimer's disease plaque and in Parkinson's disease Lewy bodies. Using single-molecule methods to directly construct binding-folding maps (as in the current work) will be a critical component of this future effort, and also should be widely applicable to other intrinsically disordered or amyloid-forming proteins.

More information: "Interplay of α-synuclein binding and conformational switching probed by single molecule fluorescence," *PNAS*.

Source: The Scripps Research Institute (news : web)