# Scientists Discern Shape of Important Protein

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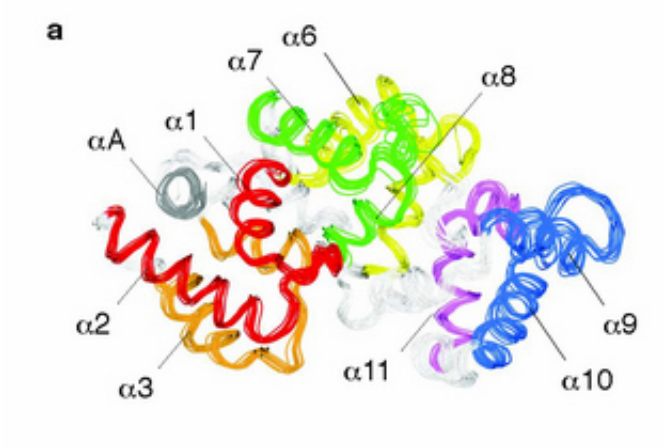


Using nuclear magnetic resonance, NC State University scientists characterized the structure of calbindin-D28K , a flexible protein linked to the prevention of neurodegenerative diseases.

Scientists at North Carolina State University have effectively lifted the veil from an important protein that is linked to the prevention of neurodegenerative diseases like Alzheimer's and Huntington's.

Dr. John Cavanagh, professor of molecular and structural biochemistry, teamed with colleagues from the Mayo Clinic and Duke University to describe the shape of the protein, calbindin-D28K. Understanding a protein's structure allows researchers to learn more about how it functions and interacts with other proteins, which, in this case, may

provide clues to developing drugs to halt the diseases.

The research appears in the July 2006 edition of *Nature Structural and Molecular Biology*.

Calbindin-D28K is a protein that either grabs calcium from areas that have too much or serves as an on/off switch for further chemical reactions. It is known for its flexibility; it is found in the kidneys, pancreas, ocular nerve and in abundant quantities in the brain. Recent studies show, Cavanagh says, that it acts as a bodyguard in the brain, binding to and inhibiting caspase-3, a protein that stimulates plaque formation and tangle formation, which are hallmark characteristics of neurodegenerative disease. Until now, however, the structure of calbindin-D28K remained a mystery.

“If you don’t know the shape of the protein, you can’t figure out how it works,” Cavanagh says. “It took a long time – about five years – but we’ve characterized the structure of this protein and found where it binds caspase-3. Insight into how it binds to caspase-3 might lead to a way of exploiting those interactions to develop therapeutics.”

It took a long time to characterize calbindin-D28K, Cavanagh says, because it was initially a challenge to force cells to make enough protein in order to do the requisite studies. Additionally, many parts of the protein are very similar and so are extremely difficult to distinguish from each other.

The research team used nuclear magnetic resonance to get a high-resolution picture of what the protein looks like. In this painstaking technique – occurring inside machines that have magnetic fields several hundred times greater than the Earth’s magnetic pull – radio waves are bounced off the approximately 5,000 nuclei in the protein.

“When you hit a nucleus with a radiofrequency pulse, it resonates, sort of making its own little noise, like a tuning fork,” Cavanagh says. “The frequency at which the nuclei resonate after being hit with a pulse is very specific to their specific position in the protein. So after we hit all of them with a pulse, it’s like hitting all the keys of a piano at the same time and it’s just an awful mess. And remember, we’re doing this for 5,000 separate keys. Yet, we’re able to untangle this mess to find the specific frequency of each nucleus and relate that to where it lies in the protein.”

Cavanagh isn’t satisfied with this knowledge, however. He says the shape-shifting protein sometimes contains no calcium. When it grabs calcium, it changes its shape.

“This could be why the protein plays so many different roles,” Cavanagh says. “Proteins that change shape usually serve as on/off switches, but this protein also grabs calcium and takes it elsewhere. Now we’re working to determine the structure of this protein when it has no calcium.”

Source: North Carolina State University