Protein plays Jekyll and Hyde role in Lou Gehrig's disease

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Amyotrophic lateral sclerosis (ALS), more commonly known as Lou Gehrig's disease, is a fatal neurodegenerative disease caused by the death of motor neurons in the brain and spinal cord that control muscle movements from walking and swallowing to breathing. In a groundbreaking study this week in *PLoS Biology*, Brandeis and Harvard Medical School scientists report key findings about the cause and occurrence of the familial form of ALS.

For the past three years, Brandeis chemist Jeff Agar and his colleagues have studied the rare, familial form of ALS (fALS) as a window into the sporadic form of ALS, which accounts for 90 percent of all cases.

Scientists discovered fifteen years ago that mutations in the gene that makes the protein, superoxide dismutase, are responsible for inherited ALS, but how these mutations cause ALS remain a mystery. Researchers believe deciphering the mechanisms at work in inherited ALS will clear the way to understanding and treating sporadic ALS, in large part because clinical symptoms are identical in both forms of the disease.

Agar's research demonstrated that fALS is caused by two synergistic properties of the protein superoxide dismutase, creating toxic levels of the protein in motor neurons. "We discovered that increased protein unfolding and the propensity of the proteins to aggregate, (to clump together) are the major factors in the familial form of ALS," explained Agar.

This propensity of proteins to unfold and clump together amounts to what scientists call a 'toxic gain of function.' Many diseases are caused by a loss of protein function, but some, like ALS, are linked to a gain of function in which a protein takes on a new role, unrelated to the one it is supposed to perform in healthy cells.

"The protein superoxide dismutase, normally a useful antioxidant, goes from Dr. Jekyll to Mr. Hyde when it clumps up," said Agar. This research indicates that protein aggregation is toxic in ALS, something that has not been proven for other neurodegenerative diseases such as Alzheimer's and Parkinson's, though researchers worldwide are studying the role of protein clumps in these conditions, as well.

Still, scientists disagree on the nature of the toxic gain of function because not all clumps are toxic, nor are they all the same size in patients with neurodegenerative disease, or healthy people, for that matter. But Agar says that large clumps cause cell death, literally exploding the thread-like axons on nerve cells that transmit impulses from the cell.

"Most people are familiar with the process of aggregation, which is what happens when you cook an egg. A fluid (the egg white) is full of proteins that are free to move about. Upon cooking, these proteins unfold and clump together. When this happens inside a cell, especially inside the long, narrow, tubes that connect neurons (axons), the cells essentially choke because they can't move proteins and nutrients to where they are needed. The loss of motor neurons then results in the death of ALS patients."

The next step, said Agar, is to develop drugs that target key proteins and prevent them from clumping together. "Our study used data from innumerous ALS researchers, and the field has been working toward this discovery for some time. My hope is that if our findings are validated by other research groups, molecules that prevent aggregation will be

developed and used to treat ALS. We hope to contribute to this process and have initiated the lengthy process of developing such molecules in collaboration with the laboratories of Greg Pestko and Dagmar Ringe here at Brandeis."

Source: Brandeis University

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