

Purdue researchers reveal role of protein mutation in Parkinson's disease

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Purdue University researchers revealed how a mutation in a protein shuts down a protective function needed to prevent the death of neurons in Parkinson's disease, possibly opening the door to new drug strategies to treat the disorder.

Fred Regnier, the J.H. Law Distinguished Professor of Chemistry, and Jean-Christophe Rochet, an associate professor of [medicinal chemistry](#) and [molecular pharmacology](#), led the team that discovered how the protein DJ-1, which plays a significant role in protecting [neurons](#) from damage, is shut down by a subtle mutation.

A substitution in one link of the chain of [amino acids](#) that makes up the protein renders it unable to be activated to protect neurons from the build up of protein "aggregates," or "clumps," that lead to cell death in those with [Parkinson's disease](#).

"The saying that you are only as strong as your weakest link appears to hold true in the case of the chain of amino acids that make up a protein," Regnier said. "The magnitude of the effect of this subtle change is surprising. It can make the difference between having a disease and being healthy."

According to the Parkinson's Disease Foundation, an estimated 7 million to 10 million people worldwide are living with the disease, which is a [neurodegenerative disorder](#) that causes muscular rigidity, slowness of movement, poor balance and tremors. The death of neurons in a region

of the brain called the substantia nigra cause the symptoms.

The findings of the Purdue-led study could potentially lead to new Parkinson's treatments, Rochet said.

"The current methods of treatment are to add back what the lost cells used to produce, similar to hormone replacement therapies," he said. "Understanding this error in a key protein could help researchers find a way to prevent [cell death](#) in the first place. Perhaps a compound could be found that could correct the problem and resurrect the protective function of the protein. Of course interventions would be needed in many places to treat the disease, but this could be one of several places to target for a potential treatment."

When functioning properly, DJ-1 appears to serve as a "chaperone" protein for the neural protein alpha-synuclein, escorting and protecting it as it performs its biological task. Without the help of DJ-1, alpha-synuclein can unfold and expose sticky surfaces that cause it to clump together with other proteins. These [clumps](#) are a component of the "Lewy bodies" and other protein deposits that build up in the neurons of Parkinson's disease patients and cause the cells to die, he said.

About 10 years ago it was discovered that people with familial, early-onset Parkinson's disease had a mutation in the gene that encodes DJ-1 that leads to a mutant form of the protein through a substitution in one of the protein's amino acids.

The Purdue-led team developed a new quantitative mass spectrometry approach to evaluate and compare the mutant and normal protein. They discovered that the substitution prevents DJ-1 from undergoing an important chemical reaction in which oxygen is added to a specific site on the protein. This addition of oxygen takes the protein into a two-oxygen form that facilitates its chaperone function.

It had been thought that the amino acid substitution led to an unfolding of the protein, but the team found that it instead slightly alters the structure of the active site pocket, preventing the addition of oxygen at that site.

In addition the team found that the attachment of too much oxygen or an oxygen atom linked at the wrong location also disabled the protein's protective abilities, Rochet said.

"The interaction of this protein with oxygen needs to be very precise," Rochet said. "We need just enough oxygen added at just the right site to activate the protective ability of the protein, but too much oxygen or oxygen added at the wrong location causes real problems."

Because the precise oxidation of the [protein](#) may play a significant role in preventing the development of Parkinson's disease, evaluation of the levels of oxidized DJ-1, non-oxidized DJ-1 and over-oxidized DJ-1 could be the starting point of a new diagnosis method, Regnier said.

"Mass spectrometers could be used to find specific forms of DJ-1 and changes in the levels of these different forms could lead to a diagnosis of the disease," he said. "If we could find that a certain form or ratio appears early in disease development, we might be able to catch it and treat it earlier."

The team's findings are detailed in a paper in the February issue of the journal *Molecular and Cellular Proteomics*. In addition to Regnier and Rochet, paper co-authors include postdoctoral research associate Ashraf G. Madian and graduate student Naomi Diaz-Maldonado of the Purdue Department of Chemistry; graduate students Jagadish Hindupur and Vartika R. Mishra and former graduate student John D. Hulleman of the Purdue Department of Medicinal Chemistry and Molecular Pharmacology; and Emmanuel Guigard and Cyril M. Kay from the

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Provided by Purdue University

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