A new tool for understanding Parkinson's disease
2 April 2015, by Nik Papageorgiou

EPFL scientists have developed a new method that can accurately simulate the chemical modification of the protein behind Parkinson's disease. The technique, has opened a new way of understanding Parkinson's, and can be expanded to other proteins and diseases as well.

Parkinson’s disease is characterized by the aggregation of the protein alpha-synuclein in brain cells that control movement, giving rise to the disease’s symptoms. Evidence suggests that alpha-synuclein begins to aggregate when it undergoes a chemical process where nitrogen groups are attached to four of its amino acids. This process, called nitrification, has been impossible to study in the lab. The problem is that current nitrating methods generate non-homogeneous mixtures of alpha-synucleins that are nitrated at different amino acid sites. As a result, the proteins have different properties to natural alpha-synuclein, and cannot be used effectively to mimic and study what happens in Parkinson’s disease.

The exact causes of Parkinson's disease, which affects around ten million people worldwide, are still unclear. But one place to look is the protein alpha-synuclein, which begins to clump together inside brain cells to form long fibrils, which then evolve into aggregates that eventually destroy the cell. This has been linked to a several chemical modifications of alpha-synuclein, one of which is nitrification, where nitrogen groups attach to its tyrosine amino acids.

However, nitration of alpha-synuclein has proven hard to study in the lab. The problem is that current nitrating methods generate non-homogeneous mixtures of alpha-synucleins that are nitrated at different amino acid sites. As a result, the proteins have different properties to natural alpha-synuclein, and cannot be used effectively to mimic and study what happens in Parkinson’s disease.

The new method produced a completely...
homogenously nitrated or tailored mixture of nitrated alpha-synuclein. When tested in in vitro, the modified proteins lost their ability to interact properly with vesicles, such as those found in cells. Further tests also showed that site-specific nitration changed alpha-synuclein's structure, which directly influences the protein's tendency to form the aggregates seen in Parkinson's disease.

Tools that shape the future

Hilal Lashuel's team has been working on chemical modifications of alpha-synuclein and other proteins for over five years. This method is the latest achievement in this line, overcoming the last barrier, nitration. "These advances allow us now to reconstruct, in vitro, a-synuclein species with the same chemical properties as those isolated from diseased human brains," says Hilal Lashuel. Since the normal functions of alpha-synuclein are still a mystery, being able to reconstruct its chemical properties as they exist in the human brain may also open new avenues for understanding its biological role, and how it can become impaired in disease.

The new method is not limited to alpha-synuclein, but can be used across different proteins and different types of chemical modifications, which often underlie a multitude of diseases. Just in the context of Parkinson's disease, Lashuel anticipates that the chemical tools his group has developed will have an tremendous impact: "These advances will facilitate the development of antibodies and imaging agents for the detection and quantification of different a-synuclein species and aggregates along the progression of Parkinson's disease, which could lead to novel approaches for its diagnosis and treatment."

More information: "Elucidating the role of site-specific nitration of -synuclein in the pathogenesis of Parkinson's disease via protein semisynthesis and mutagenesis." JACS 13 March 2015. DOI: 10.1021/ja5131726

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