Study raises doubts on a previous theory of Parkinson's disease

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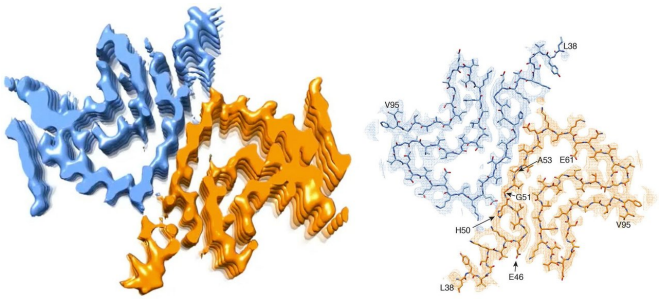

Cross section of an alpha-synuclein fibril. Left: 3D reconstruction of the fibril, showing two interacting protein molecules. Right: atomic model of the fibril structure. Credit: Universität Basel

Parkinson's disease was first described by a British doctor more than 200 years ago. The exact causes of this neurodegenerative disease are still unknown. In a study recently published in *eLife*, a team of researchers led by Prof. Henning Stahlberg from the Biozentrum of the University of Basel has now questioned the previous understanding of this disease.

The arms and legs tremble, the muscles become weaker and the movements slower ? these are typical symptoms that many Parkinson's patients suffer. More than 6 million people are affected worldwide. In these patients, the dopamine-producing nerve cells in the brain slowly die off. The resulting lack of this neurotransmitter impairs motor function and often also affects the cognitive abilities.

Questionable: Protein fibrils cause Parkinson's disease

It has been assumed that the protein alpha-synuclein is one of the trigger factors. This protein can clump together and form small needles, so-called fibrils, which accumulate and deposit as Lewy bodies in the nerve cells. These toxic fibrils damage the affected brain cells. A team of scientists led by Prof. Henning Stahlberg from the Biozentrum of the University of Basel, in collaboration with researchers from Hoffmann-La Roche Ltd. and the ETH Zurich, have now artificially generated an alpha-synuclein fibril in the test tube. They have been able to visualize for the first time its three-dimensional structure with atomic resolution. "Contrary to our expectations, the results seem to raise more questions than they can hope to answer," says Stahlberg.

It is important to know that in some congenital forms of Parkinson's disease, affected persons carry genetic defects in the alpha-synuclein gene. These mutations, it is suspected, eventually cause the protein to fold incorrectly, thus forming dangerous fibrils. "However, our 3-D structure reveals that a mutated alpha-synuclein protein should not be able to form these type of fibrils," says Stahlberg. "Because of their location, most of these mutations would rather hinder the formation of the fibril structure that we have found." In brief, if the fibril structure causes Parkinson's disease, the genetic defect would have to protect against the disease. But this is not the case. So, it could be possible that a different type of fibril or another form of the protein triggers the disease in these patients.

More investigations are now needed to understand this fibril structure. What are the effects of the alpha-synuclein mutations? Do they lead to distinct forms of protein aggregates? What is the role of the fibrils for the nerve cells, and why do these cells die? To date, the exact physiological function of alpha-synuclein is still not known. Since only the symptoms of this neurodegenerative disease can be alleviated with the current medications, new concepts are urgently needed.

More information: Ricardo Guerrero-Ferreira et al. Cryo-EM structure of alpha-synuclein fibrils, *eLife* (2018). DOI: 10.7554/eLife.36402

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