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"Molecular switch" discovered in Parkinson's protein

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In one variant of Parkinson's disease, the enzyme LRRK2 plays a central role. Scientists at the University of Kassel have now discovered a mechanism that controls the activity of LRRK2. This opens up new approaches for the development of drugs to counter the disease, which until now is incurable.

Following Alzheimer's, Parkinson's disease is the most frequently occurring neuro-degenerative illness. It is estimated that approximately 7 million people suffer from the disease worldwide. A portion of these cases have a hereditary basis and are caused by mutations in specific genes. These so-called familial Parkinson's variants occur with varying degrees of frequency in different ethnic groups; certain mutations are particularly widespread in Italy and Spain, for example. Mutations of a protein called LRRK2 are seen as the most frequent cause of inherited Parkinson's disease.

A research group with scientists from Kassel University has now discovered the "molecular switch" that controls the activity of this protein. "Our results can show ways to develop new drugs to regulate the activity of this protein and thus provide new approaches for the treatment of inherited Parkinson's disease," explains Prof. Dr. Friedrich W. Herberg, head of the Department of Biochemistry at Kassel University. "It may also be possible to derive approaches for the treatment of other variants of Parkinson's from these results."

The protein LRRK2 is also called "dardarin" from the Basque term

"dardara" which means "to tremble". In human cells, the protein has a mediating function as it delivers phosphates to other proteins. Dardarin has a special and until now not fully clarified role in certain cells of the midbrain which produce the neurotransmitter dopamine. These cells in the midbrain die in persons suffering from Parkinson's. The resulting lack of dopamine leads to the well-known Parkinson's symptoms such as muscle tremors, depression or the loss of the sense of smell.

The Kassel researchers have investigated individual areas of the enzyme dardarin very closely. "Proteins are made up of smaller building blocks – amino acids. We were able to determine that in dardarin mutations, which are taken to be responsible for inherited Parkinson's, the phosphate supply is disturbed in an area around the amino acid 1441," explains Dipl. Biol. Kathrin Muda, one of the authors of a study that has now appeared in the journal *Proceedings of the National Academy of Science*. "In particular, we found that an additional protein called a 14-3-3 protein can bind in the area 1441 and thus have an effect on the activity of dardarin. In the mutated variants the binding at the dardarin enzyme is disturbed and the activity of dardarin is no longer correctly regulated." How this then results in the dying off of cells in the middle brain is not yet known. "If a way is found to substitute the binding with 14-3-3 through another mechanism that takes the place of the mutated dardarin variants, then we will have taken a big step in the development of anti-Parkinson's drugs," says Muda.

In cooperation with scientists from Tübingen University, from the Helmholtz Center Munich and the German Cancer Research Center Heidelberg, the Kassel researchers make use of so-called mass spectrometry, a process for the weighing of atoms and molecules. Through a comparison of the weight of normal and mutated LRRK2 protein particles, it was possible to draw conclusions about the phosphate supply process in the cells.

One of the focal points of the working group at Kassel University in their research is investigations of protein kinase A, one of the enzymes that is involved as a mediator in many processes in human cells, as for instance with the phosphate supply of LRRK2. In addition to Herberg and Muda, the Kassel scientists Dr. Daniela Bertinetti and Dipl. Biol. Jennifer Sarah Hermann as well as Dr. Frank Gesellchen from Glasgow were also involved in the research efforts. The Biochemistry Department of Kassel University is part of a consortium for research of human proteins (www.affinomics.org). The study received support from the EU, the Otto Braun Fund and the foundation of the actor Michael J. Fox, a sufferer of Parkinson's disease, among other sources.

More information: 'Parkinson-related LRRK2 mutation R1441C/G/H impairs PKA phosphorylation of LRRK2 and disrupts its interaction with 14-3-3' Kathrin Mudaa, Daniela Bertinettia, Frank Gesellchenb, Jennifer Sarah Hermanna, Felix von Zweydorfc, Arie Geerlofd, Anette Jacobe, Marius Ueffing, Christian Johannes Gloecknerc, Friedrich W. Herberga. *PNAS* www.pnas.org/content/early/201 … /1312701111.abstract

Provided by Kassel University