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Parkinson's disease: Parkin protects from neuronal cell death

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Researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich identify a novel signal transduction pathway, which activates the parkin gene and prevents stress-induced neuronal cell death.

Parkinson's disease is the most common movement disorder and the second most common neurodegenerative disease after Alzheimer's disease. It is characterized by the loss of dopamin-producing neurons in the substantia nigra, a region in the midbrain, which is implicated in motor control. The typical clinical signs include resting tremor, muscle rigidity, slowness of movements, and impaired balance. In about 10% of cases Parkinson's disease is caused by mutations in specific genes, one of them is called parkin.

"Parkinson-associated genes are particularly interesting for researchers, since insights into the function and dysfunction of these genes allow conclusions on the pathomechanisms underlying Parkinson's disease", says Dr. Konstanze Winklhofer of the Adolf Butenandt Institute at the LMU Munich, who is also affiliated with the German Center for Neurodegenerative Diseases (DZNE). Winklhofer and her colleagues had previously observed that parkin can protect neurons from cell death under various stress conditions. In the course of this project, it became obvious that a loss of parkin function impairs the activity and integrity of mitochondria, which serve as the cellular power stations. In their latest publication, Winklhofer and coworkers uncovered the molecular mechanism that accounts for parkin's neuroprotective action.

"We discovered a novel signaling pathway that is responsible for the neuroprotective activity of parkin," Winklhofer reports. The central player of this pathway is a protein called NEMO, which is activated by the enzymatic attachment of a linear chain of ubiquitin molecules. This reaction is promoted by parkin, thereby enabling NEMO to activate a signal cascade, which ultimately leads to the expression of a specific set of genes. Winklhofer's team identified one essential gene targeted by this pathway, which turned out to code for the mitochondrial protein OPA1. OPA1 maintains the integrity of mitochondria and prevents stress-induced neuronal cell death.

"These findings suggest that strategies to activate this signal pathway or to enhance the synthesis of OPA1 in cells exposed to stress could be of therapeutic benefit," Winklhofer points out.

The newly identified signal pathway may also be relevant in the context of other neurological conditions that are characterized by the loss of specific neurons. Konstanze Winklhofer and her group are already engaged in further projects designed to determine whether other molecules regulated by this pathway might provide targets for therapeutic interventions.

Provided by Ludwig Maximilian University of Munich

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