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Parkinson's protein protects neurons from stress induced cell death

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The scientists could show that Parkin prevents the induction of neuronal cell death. As reported in the *Journal of Neuroscience*, the protein activates a survival mechanism which had been known for its prominent role in immune response.

Usually, Parkinson's disease occurs after the age of 50 and in Germany about 400,000 people are affected. It is characterized by a decline of neurons in the so-called Substantia Nigra, a structure in the midbrain that produces dopamine. The resulting deprivation of this messenger substance causes symptoms like muscular tremor at rest and restricted mobility and even complete immobility. Characteristic deposits are found in the brain, the Lewy corpuscles.

Little is known about the causes of Parkinson's disease. It has only been known for a few years that ten to fifteen per cent of all cases are associated with mutations in certain genes.

"The parkin gene is of special interest here", says Winklhofer. "One effect of its inactivation is that the Parkin protein loses its physiological function. This genetic defect plays a role for hereditary Parkinson's disease, which may lead to an early onset of the disease."

However, inactivation of the Parkin protein could also contribute to sporadic forms of the disease. In these cases massive oxidative stress probably results in misfolding and aggregation of the protein. "Interestingly, misfolding of Parkin proteins has recently been observed

in the brain of patients with sporadic Parkinson's disease", Winklhofer reports.

The scientists could now show in their study that Parkin protects the neuronal cells by mediating the activation of the nuclear protein NF-êB ("Nuclear Factor-kappaB"). This protein is known for triggering a survival programme in many human cells, which prevents cell death under stress conditions. The experiments indicate that mutations in the parkin gene result in an impaired activation of NF-êB.

"This, however, promotes an enhanced susceptibility of neurons to stress-induced cell death", says Winklhofer. "Further studies will now have to show whether these findings about the function of Parkin in the activation of cellular survival programmes can contribute to the development of new strategies for the treatment of Parkinson's patients."

Citation: "Parkin mediates neuroprotection through activation of IKK/NF-kB signaling", Henn, I.H., Bouman, L., Schlehe, J.S., Schlierf, A., Schramm, J.E., Wegener, E., Nakaso, K., Culmsee, C., Berninger, B., Krappmann, D., Tatzelt, J., and Winklhofer, K.F. *Journal of Neuroscience*, 27, 1868-1878, 2007

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