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Science

The characteristic pathological signs of PD are the loss of dopaminergic (DA) neurons in the substantia nigra (SN) and presence of protein inclusions called Lewy bodies in the substantia nigra. Dominant missense mutations in LRRK2 have been identified that cause familial forms of PD. LRRK2 and its closest relative LRRK1 belong to the ROCO protein superfamily. It is unknown whether these proteins are functionally redundant. Nevertheless, it has recently been shown that LRRK2 and LRRK1 can form heterodimers. In addition, it has been shown that LRRK1 mutations might contribute to earlier onset of symptoms in LRRK2 G2019S patients. LRRK1 and LRRK2 are multidomain proteins consisting of a leucine rich repeat region (LRR), a Ras of complex gtpase domain (ROC), a C-terminal of Roc (COR) domain, a Serine/Threonine kinase domain and a WD40 domain. The most common LRRK2 mutation found in PD patients is a G2019S substitution that appears to result in increased LRRK2 kinase activity. Several potential substrates and interacting proteins have been identified for LRRK2 but these findings require further validation in more physiological paradigms. Subcellular localization studies on LRRK2 indicate that LRRK2 is present at synapses, where it might be involved in the endosomal-autophagic pathway.

Based on these data, we hypothesize that LRRK2 associates with the endocytotic machinery, and is required for synaptic vesicle recycling in neurons. PD associated LRRK2 mutations result in defects of dopamine recycling at synapses of SN neurons in the striatum, leading to increased extracellular DA levels causing excitotoxic loss of DA

neurons. The late onset of LRRK2 associated PD might be explained by compensatory LRRK1 function.

To test this hypothesis, we initially compared LRRK2 knockout and wildtype mice using biochemical and cellular paradigms. This has lead to the identification of proteins involved in endocytosis that were less phosphorylated in LRRK2 knockout mice compared to wildtype mice. We also addressed whether LRRK1 can compensate for loss of LRRK2 function, by siRNA knockdown of LRRK1 in LRRK2 knockout and wildtype cells and analyzing the phosphorylation status of the previously identified proteins.

These data show that LRRK2 is involved in the phosphorylation of endocytosis associated proteins. Functional consequences of this phosphorylation event and whether LRRK2 can phosphorylate these proteins directly will be analyzed in future experiments. We are confident that our research will give more insight into the physiological function of LRRK2 and hope that this knowledge will contribute to the elucidation of the etiology of PD.

Selected publication

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