Function and activation mechanism of LRRK2 and the understanding of Parkinson’s disease

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Country

Netherlands

Title of project or programme

Function and activation mechanism of LRRK2 and the understanding of Parkinson's disease

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NWO

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5.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
Parkinsons Disease (PD) is a neurodegenerative disorder affecting more than five million people worldwide. Recently a number of genetic factors causing PD have been discovered. Mutations in human leucine-rich-repeat kinase 2 (LRRK2) have been found to be thus far the most frequent cause of late-onset PD. LRRK2 belongs to the Roco family of proteins, which are characterized by the presence of a Ras-like G-domain (Roc), a C-terminal of Roc domain

(COR), and a kinase domain. Importantly, PD mutations in LRRK2 are linked to decreased GTPase and enhanced kinase activity, suggesting a possible PD-related gain of abnormal function.

The aim of this project is to elucidate the activation mechanism of LRRK2 and thereby contribute to the understanding of the biochemical pathways responsible for LRRK2-linked PD, which may help to identify therapeutic targets for PD.

Important progress on the understanding of the complex regulatory mechanism of LRRK2 has come from our work with related Roco proteins from lower organisms. Our atomic structure of the Roco protein from Chlorobium tepidum revealed that Roco proteins belong to the GAD class of molecular switches (G proteins activated by nucleotide dependent dimerization). As in LRRK2, PD-analogous mutations in Roco proteins from Chlorobium and Dictyostelium decrease the GTPase reaction. The structure of Dictyostelium discoideum Roco4 kinase was obtained for wild-type and PD mutants, and explains the G2019S related increased LRRK2 kinase activity.

The focus of this project will be 1) the complex intramolecular LRRK2 activation mechanism, 2) mechanism and regulation of dimerization and 3) identify the input/output and activation mechanism of LRRK2. These experiments will be performed with Roco proteins from lower organisms and combined with data from wild type and mutant LRRK2.

Lay Summary
Further information available at:

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Investments > €500k

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Netherlands

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Parkinson's disease & PD-related disorders

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