

A novel two-step model for neurodegeneration in Parkinson's disease

<https://www.neurodegenerationresearch.eu/survey/a-novel-two-step-model-for-neurodegeneration-in-parkinson%c2%92s-disease/>

Principal Investigators

Institution

Contact information of lead PI

Country

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A novel two-step model for neurodegeneration in Parkinson's disease

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Research Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder primarily caused by the progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN). Despite the advances in gene discovery associated with PD, the knowledge of the PD pathogenesis is largely limited to the involvement of these genes in the generic cell death pathways, and why degeneration is specific to DA neurons and why the degeneration is progressive remain enigmatic. Broad goal of our work is therefore to elucidate the mechanisms underlying specific and progressive DA neuron degeneration in PD. Our new *Drosophila* model of PD ?Fer2 gene loss-of-function mutation? is unusually well suited to address these questions. Fer2 mutants exhibit specific and progressive death of brain DA neurons as well as severe locomotor defects and short life span. Strikingly, the death of DA neuron is initiated in a

small cluster of Fer2-expressing DA neurons and subsequently propagates to Fer2-negative DA neurons. We therefore propose a novel two-step model of the neurodegeneration in PD: primary cell death occurs in a specific subset of dopaminergic neurons that are genetically defined, and subsequently the failure of the neuronal connectivity triggers and propagates secondary cell death to remaining DA neurons. In this research, we will test this hypothesis and investigate the underlying molecular mechanisms. This will be the first study to examine circuit-dependency in DA neuron degeneration. Our approach will use a combination of non-biased genomic techniques and candidate-based screening, in addition to the powerful Drosophila genetic toolbox. Furthermore, to test this hypothesis beyond the Drosophila model, we will establish new mouse models of PD that exhibit progressive DA neuron degeneration. Outcome of this research will likely revolutionize the understanding of PD pathogenesis and open an avenue toward the discovery of effective therapy strategies against PD.

Lay Summary

Further information available at:

Types:

Investments > €500k

Member States:

European Commission

Diseases:

Parkinson's disease & PD-related disorders

Years:

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Database Categories:

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