Modelling idiopathic Parkinson’s disease-associated somatic variation in dopaminergic neurons – ATTRACT

https://neurodegenerationresearch.eu/survey/modelling-idiopathic-parkinsons-disease-associated-somatic-variation-in-dopaminergic-neurons-attract/

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Luxembourg

Title of project or programme

Modelling idiopathic Parkinson's disease-associated somatic variation in dopaminergic neurons - ATTRACT

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FNR

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01/01/2016

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5.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
Background: Parkinson’s disease (PD) is characterized by a selective loss of dopaminergic neurons, Lewy body formation and respiratory chain (RC) complex I (CI) deficiency in the

substantia nigra (SN). In idiopathic PD (IPD), neurohistology studies link RC dysfunction to somatic deletions in mitochondrial DNA (mtDNA). However, the mechanisms leading from RC dysfunction to neurodegeneration remain unknown and no treatment (reverting, stopping or at least slowing this decline) is currently available. This is due to the lack of endogenous cellular systems which recapitulate somatic phenotypes of the IPD SN and allow monitoring of disease-associated changes over time thereby facilitating therapeutic tests. Preliminary results: The role of mitochondrial genome integrity in IPD was studied, quantifying mtDNA deletions/copy number and protein abundance of RC CI-IV in dopaminergic neurons from IPD patient and control midbrain sections. Real-time PCR analysis in individually laser-captured SN neurons identified mtDNA depletion as cause of CI deficiency. In conjunction, protein levels of mtDNA-associated mitochondrial transcription factor A and 2B correlated with CI abundance in single neurons. Objective: To design a patient-derived cellular IPD model which enables longitudinal studies of somatic changes in mitochondrial DNA integrity and RC function by combing ‘omics’ readouts from postmortem midbrain with iPSC (induced pluripotent stem cell) technology. Hypotheses: Work package (WP) A: (i) MtDNA mutations/depletion cause RC dysfunction which in turn triggers degeneration of dopaminergic neurons in IPD. (ii) Signaling pathways associated with this process can be identified in human midbrain sections. WP B: (iii) Mitochondrial phenotypes mirroring IPD SN pathology develop during long-term culture of CI-deficient iPSC-patient neurons. (iv) The fate of dopaminergic neurons in IPD is determined by the extent of RC dysfunction in these cells. (v) MtDNA depletion in IPD patient neurons induces RC deficiency firstly affecting CI and subsequently involving CIV and CIII. (vi) IPSC-derived IPD patient neurons recapitulate RC deficiency-associated pathways identified in postmortem tissue. WP C: (vii) Integration of metabolomics data from iPSC-neurons permits in silico modelling of mtDNA disintegration and RC dysfunction in IPD. Methods: WP A: Neuromelanin-positive SN neurons will be isolated from frozen control and IPD patient midbrain sections with laser capture microdissection, pooled (to increase RNA yield) and prepared for transcriptomic analysis. Controls and patients will be stratified according to CI mRNA levels. RNA profiles in SN neurons will be compared between “CI extreme” cases (to decrease inter-individual heterogeneity and improve signal-to-noise ratios) within and across patient and control groups. WP B: CI-deficient patient and CI-“super” normal control iPSC-neurons (“extreme” cases) will be cultured (?300d) and mRNA profiles of IPD-associated genes/pathways identified in WP A will be followed longitudinally. RC complex activities/abundance, mtDNA and mitochondrial function will be studied in-depth in single and pooled neurons to determine the relevance of age-related somatic changes in IPD. WP C: Further characterization of IPD pathways will be achieved by GC/MS detection of metabolites of the central carbon metabolism in iPSC-neuron cultures. Metabolomics data will be used to derive a computational model of the interplay between RC deficiency/mtDNA depletion and mitochondrial biochemistry.

Lay Summary
Further information available at:

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Investments > €500k

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Luxembourg

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N/A

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