Computational prediction of biochemical compensatory mechanisms in subjects at risk of developing Parkinson’s disease.

https://neurodegenerationresearch.eu/survey/computational-prediction-of-biochemical-compensatory-mechanisms-in-subjects-at-risk-of-developing-parkinsons-disease/

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Research Abstract
There is a pressing need to discover new treatments capable of slowing neurodegenerative progression in Parkinson’s disease (PD). There are many risk factors that are known to increase one’s probability of developing PD, e.g., mutations in GBA encoding beta-glucocerebrosidase, an enzyme in lipid metabolism, is found in 8-14% of autopsy-proven PD diagnoses. However, not all at-risk individuals go on to develop PD. A hallmark of PD is degeneration of dopaminergic

neurons in the substantia nigra pars compacta (DN) leading to the classical motor symptoms enabling clinical diagnosis. Within DN of at-risk but healthy subjects, we hypothesise the existence of metabolic compensatory mechanisms that are neuroprotective and furthermore that we can predict the mechanisms of compensation using computational models of metabolism in healthy, at risk and diseased DN. We will reconstruct DN relevant lipid metabolic pathways, then refine and validate the reconstruction by comparison with existing and new lipidomic data generated, in collaboration with analytical chemists, from human dopaminergic neurons in vitro, derived from induced pluripotent stem cells, using standard protocols. This DN lipid reconstruction will be integrated with parallel DN reconstruction efforts within the Systems Biochemistry Group in order to generate a comprehensive, accurate, constraint-based model of DN metabolism. Computational modelling will be used to predict stratification of at-risk subjects prior to treatment with existing candidate neuroprotectants and compared with the response of individual at-risk subjects in clinical studies. Furthermore, the computational model shall be used to predict novel metabolic compensatory mechanisms that confer neuroprotection in silico. These predictions shall be used to accelerate the experimental efforts within the LCSB to discover novel neuroprotectants, e.g., the selection of candidate compounds for in vitro screens and in vivo murine tests for neuroprotective efficacy.

Further information available at:

https://www.fnr.lu/projects/computational-prediction-of-biochemical-compensatory-mechanisms-in-subjects-at-risk-of-developing-parkinsons-disease-2/

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