Genome-scale exploration of flux distributions for dopaminergic neurons in Parkinson’s disease

https://www.neurodegenerationresearch.eu/survey/genome-scale-exploration-of-flux-distributions-for-dopaminergic-neurons-in-parkinsons-disease/

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Luxembourg

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Genome-scale exploration of flux distributions for dopaminergic neurons in Parkinson's disease

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Research Abstract

One of the hallmarks of (sporadic) Parkinson’s disease is degeneration of dopaminergic neurons in the pars compacta of the substantia nigra. The aetiopathogenesis of this degeneration is still not fully understood, with dysfunction of many biochemical pathways in different subsystems suggested to be involved. Major challenges are to (i) integrate existing experimental knowledge into a formal, self-consistent and comprehensive representation of the biochemical pathways implicated in dopaminergic neuronal degeneration, and (ii) use this

integrated representation to understand the relative contribution of dysfunction in disparate pathways to degeneration. We will generate a comprehensive reconstruction of dopaminergic neuronal metabolism by application and adaption of existing algorithms to algorithmically infer the set of biochemical reactions active in a given cell type from an existing generic reconstruction of human metabolism integrated with multiple sources of complementary high-throughput experimental data. This reconstruction will be refined by comparison of the results of (i) parallel efforts by the applicant's group to manually curate the biochemical literature on specific metabolic subsystems (central, mitochondrial and lipid metabolism as well as extracellular transport reactions specific to dopaminergic neurons), and (ii) newly generated in vitro exametabolomic and fluxomic data from induced pluripotent stem cell derived human dopaminergic neurons. The reconstruction will be converted into a constraint-based computational model of dopaminergic neuronal metabolism. Multi-objective optimization will be applied to determine the relative importance of various metabolic pathways with respect to maintenance of the normal metabolic objectives of a dopaminergic neuron, as defined during the reconstruction process. Dopaminergic neurons are known to have a high constitutive demand for energy to maintain electrophysiological activity. The applicant hypothesises that degeneration is the result of combined perturbations that impair the function of biochemical reactions that either generate or consume a large fraction of cellular energetic flux. Combinations of reactions that are sensitive to perturbation, specifically in dopaminergic neurons, will be compared with existing literature on Parkinson's disease aetiopathogenesis and used to suggest future perturbation experiments by collaborating experimental groups at the LCSB. As the predictive capacity of the computational model is highly dependent on the quality of the reconstruction, we envisage some improvement of existing algorithmic approaches to generation of cell type specific biochemical networks. As such, this project will deliver advanced open source software for automated reconstruction of human metabolic networks as well as the most comprehensive computational model of dopaminergic neuronal metabolism, validated by extensive comparison with experimental data.

Further information available at:

https://www.fnr.lu/projects/genome-scale-exploration-of-flux-distributions-for-dopaminergic-neurons-in-parkinsons-disease-2/

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