Metabolomic data-driven mechanistic computational modelling of mitochondrial dysfunction in Parkinson's disease

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1. Abstract

Patient-derived cellular models are a powerful approach to study human disease, especially neurodegenerative diseases, such as Parkinson's Disease (PD), where affected primary neurons are almost inaccessible. Nigrostriatal dopaminergic neurons are selectively vulnerable to degeneration in PD and their death is responsible for the cardinal motor symptoms. Neuroepithelial stem cell-derived models of midbrain-specific dopaminergic neurons are increasingly used for investigation of PD, which is monogenetically associated with mitochondrial dysfunction, a feature also implicated in idiopathic PD. Starting with the comprehensive generic reconstruction of human metabolism, Recon3D, we generated the first constraint-based, genome-scale, in silico model of human dopaminergic neuronal metabolism (iNESC2DN). Transcriptomic data, obtained by RNA sequencing, and quantitative exometabolomic data, obtained by targeted mass spectrometry, were generated for in vitro neuroepithelial stem cell-derived cultures and supplemented by extensive manual curation on the literature on dopaminergic neurons. The predictions of the iNESC2DN model are consistent with neurobiochemical prior information and in concordance with measured fluxes of uptake and secretion of many extracellular metabolites by dopaminergic neurons in vitro. The iNESC2DN model provides a foundation for future targeted metabolomic and tracer-based metabolomic analyses of dopaminergic neurons. We leverage it to rank order the most important metabolite concentrations to quantify to maximally reduce the uncertainty associated with current predictions of normal dopaminergic neuronal metabolism in vitro, as well as optimally design experiments to measure metabolic perturbations associated with PD. This illustrates the synergy between constraint-based computational modelling of metabolism and targeted quantitative bioanalytical chemistry.

References

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