iPSC neuronal models of Parkinson's: from pathological mechanisms to target discovery

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Résumé

Parkinson's disease (PD) is the second most common neurodegenerative disease and a major unmet clinical need in our ageing population. The Oxford Parkinson's Disease Centre (OPDC; www.opdc.ox.ac.uk) has exploited the interdisciplinary research environment within Oxford to build a translational research program to understand and target the earliest pathological pathways in PD.
In the clinic we have collected 1000 PD patients, plus age-matched controls and "at-risk" individuals for an in-depth longitudinal patient phenotyping study. In the laboratory we have generated > 200 induced pluripotent stem cell (iPSC) lines to derive dopamine neurons from PD patients and controls to allow us to study cellular phenotypes in an accurate, physiologically-relevant model of dopaminergic neurons. We have generated iPSCs from control individuals, from sporadic PD patients, and patients carrying mutations in the leucine rich repeat kinase 2 (*LRRK2*), glucocerebrosidase (*GBA*), alpha-synuclein (*SNCA*), *PINK1* or *PARKIN* genes. Mature iPSC-derived dopaminergic neurons represent a strong neurophysiological model with correct morphology, marker gene expression, electrophysiological properties, pace-making activity and spontaneous calcium flux.

We have undertaken detailed phenotypic and transcriptomic analyses of PD patient and control iPSC-derived dopamine neurons to better understand the early molecular changes which underlie cellular vulnerability in disease and to identify new targets for therapy. Our work modelling disease mechanisms has uncovered defects in the autophagic and endolysosomal pathways, in endoplasmic reticulum (ER) stress, in the biology of alpha-synuclein, in mitochondrial activity and endocytosis. Comparative transcriptomic analysis has recently allowed us to identify the regulator HDAC4 as a new potential therapeutic target and to focus on the key role of lysosomal biology in disease processes.
Finally, we have developed automated assays suitable for high-throughput screening in patient iPSC-derived neurons to target ER-stress, organelle calcium, autophagic/lysosomal pathways, mitochondrial dysfunction, and alpha-synuclein biology using state-of-the-art phenotyping platforms for target and drug discovery.

Mots-Clés: IPSC, Parkinson

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