J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

Intrinsic lrrk2 Parkinson's disease phenotypes using patient specific iPSC-derived models

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Neuroinflammation is increasingly recognized to be a crucial but poorly understood element of Parkinson's disease (PD) pathogenesis and progression. Astrocytes and microglia have inflammatory roles in injury or neurodegeneration. We previously reported that astrocytes derived from LRRK2G2019S (LRRK2) PD patient iPSCs exhibit disease phenotypes including alpha-synuclein (aSYN) accumulation and toxicity to mDa neurons. Here, we sought to confirm these phenotypes in an independent cohort. Second, we asked if LRRK2 microglia exhibit PD phenotypes. We derived astrocytes from three LRRK2-PD patient and healthy control donor iPSCs, and performed immunofluorescence (IF)and RNASeq, and co-culture with mDa neurons. We then derived microglia from this cohort and performed IF and quantitative image analysis (Imaris). Additionally, we used several phenotypic assays (phagocytosis, motility (Incucyte), cytokine analysis (Luminex)) and live imaging (iSIM super-resolution, phase contrast, and holotomography). Here we confirmed LRRK2 astrocyte-neurotoxicity in a new cohort of ISPC lines and show an increased inflammatory profile. In microglia we also identified several phenotypes in LRRK2-PD microglia: aSYN nuclear localization was increased in LRRK2-PD microglia compared to controls whereas abundance of lysosomal receptor involved in chaperone mediated autophagy, LAMP2A, was decreased. We made several observations about the development and cell biology of iPSCderived microglia and functional analyses are underway. LRRK2 mutations perturb the cell-intrinsic cell biology and function of human astrocytes and microglia, including inflammatory tone. Further studies will better define these perturbations as well as the dialog between astrocytes, microglia, and neurons.

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