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PO-090 - (23899) - ANALYSIS OF DOPAMINERGIC NEURON-SPECIFIC MITOCHONDRIAL MORPHOLOGY AND FUNCTION USING TYROSINE HYDROXYLASE REPORTER IPSC LINES

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Changes in mitochondrial function and morphology are involved in the development of many neurological diseases. *PRKN*-related Parkinson's disease (PD) is the neurodegenerative disease associated with defects in mitochondrial quality control. However, the detailed mechanism underlying the preferential degeneration of dopaminergic neurons in the substantia nigra pars compacta in PD remains unclear.

To analyze mitochondrial function and morphology specific to dopaminergic neurons, we established control and *PRKN*-mutant patient tyrosine hydroxylase reporter (*TH*-GFP) iPSC lines and performed live-cell imaging or correlative light-electron microscopy (CLEM) in GFP-expressing dopaminergic neurons derived from *TH*-GFP iPSC lines.

The live-cell imaging and CLEM analysis demonstrated that dopaminergic neurons had smaller and less functional mitochondria than non-dopaminergic neurons. Furthermore, to clarify the differences in endoplasmic reticulum-mitochondrial contact sites (ERMCS) between control and *PRKN*-mutant patient lines, we analyzed ERMCS in GFP-expressing dopaminergic neurons derived from *TH*-GFP iPSC lines using CLEM and a proximity ligation assay (PLA). The

PLA showed that the ERMCS were significantly reduced in *PRKN*-mutant patient dopaminergic neurons compared to the control. Mitochondrial calcium imaging showed that mitochondrial Ca^{2+} flux was significantly reduced in GFP-expressing *PRKN*-mutant patient dopaminergic neurons compared to the control.To analyze mitochondrial function and morphology specific to dopaminergic neurons, we established control and *PRKN*-mutant patient tyrosine hydroxylase reporter (*TH*-GFP) iPSC lines and performed live-cell imaging or correlative light-electron microscopy (CLEM) in GFP-expressing dopaminergic neurons derived from *TH*-GFP iPSC lines.
These results suggest a defect in calcium flux from ER to mitochondria is due to the decreased ERMCS in *PRKN*-mutant patient dopaminergic neurons.

Palavras-chave : Parkinson's disease, iPS cells, dopaminergic neurons