Background

- Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) and the formation Lewy Bodies (LB) throughout the brain.
- Optineurin (OPTN) is a protein critical for autophagy, where it selectively binds cargo for degradation. OPTN mutants are associated with glaucoma and ALS.
- Braak’s Hypothesis\(^1\) is a common phenotype observed in idiopathic PD patients, where LB pathology propagates through the CNS via the vagal nerve and olfactory bulb.

Hypothesis

Following exposure to the PD neurotoxin rotenone, we expect to see perturbations to OPTN homeostasis within the cell. Moreover, impaired colocalization with LC3 may contribute to PD-associated neurodegeneration.

Methods

**Animals.** Lewis Rats dosed with 3 mg/kg/day rotenone, i.p. injection, at 24 hours, 5 days, or at end-stage (until PD-associated behavioral developments, typically 6 - 9 days). Controls were given equivalent DMSO.

**Immunohistochemistry.** High-magnification (60x) images were analyzed using ROI analysis on NIS-Elements to quantify protein expression.

**Statistics.** Data represent the mean value ± SEM. Significance (*) is p<0.05 from control, Dunn’s post hoc test after significant Kruskal–Wallis Test.

Results

**Figure 1.** OPTN and LC3 interactions are destabilized in the pedunculopontine tegmental nucleus following rotenone exposure (n = 120 – 170/group), p < 0.05.

(A-D) Representative images of control, 24 hour, 5 day, and end stage animals, respectively; 
(E) Quantification of cellular OPTN intensity (normalized to control average) shows a significant decrease at 24 h and in end stage animals using a rat-rotenone model; 
(F) Quantification of cellular LC3 intensity (normalized to control average) is observable at 24 hours post treatment

- Subcellular OPTN distribution favors punctate structures following treatment with parkinsonian neurotoxin rotenone
- OPTN – LC3 interactions are significantly destabilized in early stages of the rat-rotenone model, deemed to represent pre-clinical PD\(^2\)
- Altered OPTN intensity may correlate with a distributional shift of cellular OPTN

Future Directions

- Quantify alterations to OPTN and LC3 homeostasis in other regions vulnerable to PD pathology
- Define OPTN expression and distribution based on antibody intensity
- Elicit the role of other proteins that interact with OPTN

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