x

PARKINSON'S DISEASE & MIRO1 AS A POTENTIAL MARKER

David Nguyen MSc[1], Vinita Bharat PhD[1], Devon M. Conradson BSc[1], Pawan Nandakishore PhD[2], Xinnan Wang MD, PhD[1]

1. Department of Neurosurgery, Stanford University SOM; 2. Colaberry Inc.

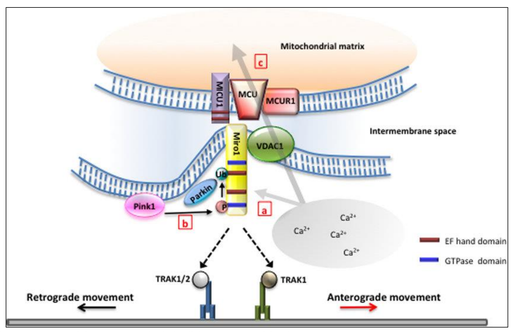
INTRODUCTION

Parkinson's disease (PD) is a debilitating, progressive nervous system movement disorder, significantly afflicting the aging population. Approximately 60,000 Americans per year are diagnosed with PD and more than 10 million people worldwide are living with PD. PD is characterized by the selective loss of dopaminergic neurons in the substantia nigra, although its pathogenesis remains to be elucidated.

https://www.pcori.org/sites/default/files/PCORI-Story-Women-Parkinsons-Disease-Nov2019-Motor-Nonmotor-Symptoms-799x905.png

Mitochondrial dysfunction has been implicated in predisposing neurons to PD-linked pathology. Miro1 (Mitochondrial Rho GTPase 1) is encoded by the *RHOT1* gene on chromosome 17 and is an outer mitochondrial membrane protein that aids mitochondrial movement by tethering the mitochondria to the motor/adaptor complex.

Miro1 is integral to mitochondrial apoptosis and homeostasis. Eliminating Miro1 from the surface of damaged mitochondria is a requirement for mitochondrial clearance via mitophagy. Furthermore, PD proteins LRRK2, PINK1, and Parkin are molecular companions that aid the removal of Miro1 from aberrant mitochondria that are destined for mitophagy.

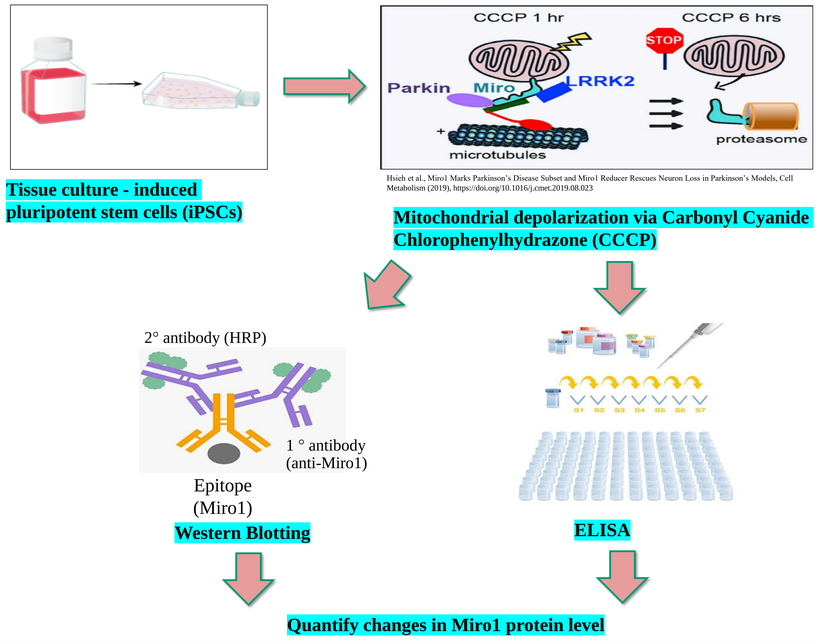


https://www.semanticscholar.org/paper/Mitochondrial-trafficking-in-neurons-and-the-role-Birsa-Norkett/db958b008c66c7043f07edfd0ffe5172932191/figure/0

Molecular machinery involved in mitochondrial movement

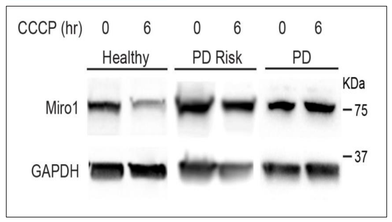
There is a lack of reliable molecular markers for Parkinson's disease patients and at-risk individuals. The detection of the pre-symptomatic population of PD will empower more effective clinical intervention to delay or prevent disease onset. We have previously discovered that Miro1 is more resistant to mitochondrial depolarization-induced degradation in fibroblasts derived from a large cohort of PD patients and several at-risk individuals. **In this study, we aim to determine whether Miro1 is useful for identifying individuals at risk for PD.**

MATERIALS & METHODS



RESULTS

Miro1 Western Blot



Representative western blot showing Miro1 levels at baseline with DMSO (0 hours) and 6 hours after depolarization with CCCP

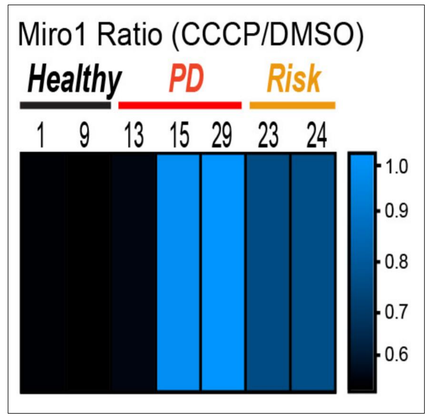
- Wild-type: "Healthy", asymptomatic genetic carrier: "PD Risk", Parkinson's Disease: "PD"
- GAPDH: protein loading control

Diagnosis	No. (Miro1 DMSO v.s. CCCP P<0.05)	No. (Miro1 DMSO v.s. CCCP P>0.05)	P (Fisher Exact) Compared to Healthy
Healthy	9 (100%)	0 (0%)	
PD	5 (16.7%)	25 (83.3%)	<0.00001
PD Risk (Carrier)	6 (14.3%)	36 (85.7%)	<0.00001
PD Risk (Hyposmia)	3 (60%)	2 (40%)	0.1099
LRRK2+, Hyposmia	1 (16.7%)	5 (83.3%)	0.002

Summary of the Western blotting results. Normalized Miro1 intensities of "with DMSO" and "with CCCP" within the same subject are compared by Student T Test, and the number of subjects with P > 0.05 together with subjects that show significant Miro1 upregulation after CCCP, or the number of subjects with P < 0.05 for Miro1 reduction after CCCP, is indicated in the column of "No. (Miro1 DMSO vs CCCP P > 0.05 or <0.05)." Fisher Exact Test is used to determine the P value of a specific group in comparison with "Healthy."

RESULTS

Miro1 ELISA



Representative ELISA heatmap. The heatmap shows the relative ratio of mean Miro1 values ("with CCCP" divided by "with DMSO") of the same subject measured by ELISA.

- **Black** – less Miro1 detected after CCCP (downregulation)
- **Blue** – similar levels of Miro1 detected after CCCP (upregulation)

CONCLUSION

- **Miro1 is resistant to degradation in 83.3% of PD patients and 85.7% of genetic risk carriers after CCCP depolarization. In all (9) healthy controls, Miro1 is NOT resistant to degradation (0%).**
- **There is a significant association of Miro1 defect with PD patients and asymptomatic genetic carriers**
- **Miro1 is a promising molecular marker for detecting both PD and at-risk populations. Tracking this Miro1 marker could aid in diagnosis and Miro1-based drug discoveries.**

FUTURE GOALS

- Longitudinal studies to determine the disease conversion rate of at-risk individuals who tested positive for the Miro1 defect.
- Investigate Miro1 phenotype in peripheral blood
- Miro1 defect also seen in several hyposmia and rapid-eye- movement behavior disorder patients: study in a larger cohort

For any questions, please contact:
David Nguyen
Medical Student | Class of 2024
LSUHSC School of Medicine – New Orleans
dngu27@lsuhsc.edu | 510.621.4133