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Drosophila in Disease Diagnosis, Mechanisms & Precision Therapy: Loss of IRF2BPL impairs neuronal maintenance via excess Wnt signal-ling

NEUROSCIENCE GRAND ROUNDS

DATE
Friday, April 28th, 2023

9:00 AM - 10:00 AM

LOCATION
Apotex Centre 050

Zoom ID: 664 3808 9041
Pass code: 526677

SPEAKER

Paul C. Marcogliese , PhD

Assistant Professor, Department of Biochemistry & Medical Genetics, Rady College of Medicine, Rady Faculty of Health Sciences, Children's Hospital Research Institute of Manitoba, University of Manitoba

BIO

Dr. Marcogliese (MAR-CO-YAY-ZEE) conducted his doctoral studies at the University of Ottawa with Dr. David Park. There, he co-developed a new mouse model of Parkinson's disease (PD) that recapitulates aspects of the human disease. Moreover, he studied the mechanism of action of the PD gene LRRK2 in Drosophila, mice, and cell culture. These studies identified the molecular pathways mediating neurode-generation implicating LRRK2 in glia as well as a neuro-immune axis in PD. Findings from his doctoral studies resulted in the publication of nine articles including first authorships in Human Molecular Genetics and PNAS. For his CIHR-funded postdoctoral studies, Dr. Marcogliese joined the lab of HHMI Investigator, Dr. Hugo J. Bellen at the Baylor College of Medicine - Neurological Research Institute. There, he mastered sophisticated genetic techniques in Drosophila such as humanization strategies to test variant function as well as emerging gene-editing techniques like CRISPR. His approach using flies to functionally discern the role of variants of uncertain significance has helped in the discovery of ten novel human neurological disease genes including first authorships published in AJHG and Nature Communications and Cell Reports. He also uncovered deeper mechanisms about the novel disease gene recently published in Science Advances.

For more information:

T: 204-235-3939
E: info@manitobaneuroscience.ca

https://twitter.com/PCMarcogliese
https://www.marcoglieselab.com/

ABSTRACT

The advent of next-generation sequencing technology has led to the identification of an increasing number of novel genes associated with neurological disorders. Functional studies in model organisms can help support diagnosis by experimentally demonstrating the disruptive impact of patient variants. Drosophila melanogaster, commonly known as the fruit fly, has been instrumental in contributing to variant testing due to its genetic strengths. In this study, we identified de novo truncating variants in the IRF2BPL (Interferon regulatory factor 2 binding protein like) gene in individuals with an undiagnosed neurodevelopmen-tal regression, resulting in the loss of skills and deterioration of cognitive and motor function. Through clinical review and studies of the ortholog in Drosophila models, we defined a novel human condition: NEDAMSS (Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures). NEDAMSS is characterized predominantly by a loss of milestones after typical development (at the mean age of 5 years) that leads to progressive ataxia, brain atrophy, and lack of mobility in adolescence. Some patients also develop dystonia and parkinsonism. We demonstrated that the IRF2BPL fly ortholog, Pits, is an essential gene in flies. However, adult-specific, neuronal reduction of Pits leads to decreased lifespan, age-dependent motor deficits, neurodegeneration, and peripheral axon loss. Loss of Pits increases Wnt1 transcript and protein in the fly brain, and excess WNT1 transcription and signaling was also observed in Irf2bpl null zebrafish and NEDAMSS patient cells. We also found that pharmacological Wnt inhibition is ameliorative in fly and fish models of IRF2BPL loss. Finally, we showed a conserved interaction of IRF2BPL with the Wnt antagonist CKIalpha. Current studies are characterizing novel Irf2bpl mouse models.

OBJECTIVES

1) Learn how humanization and overexpression strategies in flies can be used to functionally assess variant impact
in neurological disease.

2) Understand how IRF2BPL is linked to neuroregressive ataxia and is important for both development and
neuronal maintenance of time.

3) Understand how loss of IRF2BPL leads to excess WNT transcription and signaling, and how Wnt could be a
targetable pathway.

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