manitoba neuroscience network

Small molecule stabilization of protein interactions to promote axon regeneration

SEMINAR & VISITING SPEAKER SERIES

DATE
Wednesday, March 20, 2019
12:00 PM (Noon)

LOCATION
BMSB, Theatre B

SPEAKER
Alyson Fournier, Ph.D.

Professor
Faculty of Medicine
McGill University

BIO

Dr. Alyson Fournier (PhD) is a Professor in the Faculty of Medicine at McGill University in Montreal, Canada. She completed her Ph.D. in Neuroscience at McGill University (1998) and conducted her post-doctoral training at Yale University with Dr. Strittmatter working on neurodevelopment and regeneration. Since 2003 Dr. Fournier has led a research lab at the Montreal Neurological Institute studying molecular mechanisms regulating axon degeneration and regeneration.

Damaged central nervous system (CNS) neurons have a poor ability to spontaneously regenerate, causing persistent functional deficits after injury. Therapies that stimulate axon growth are needed to repair CNS damage. 14-3-3 adaptors are hub proteins that are attractive targets to manipulate cell signaling. We have identified a positive role for 14-3-3s in axon growth and have shown that fusicoccin-A (FC-A), a small-molecule stabilizer of 14-3-3 protein-protein interactions, stimulates axon growth in vitro and regeneration in vivo. Further screening of FC-A derivatives has revealed potent axon growth-promoting compounds. Through mass spectrometry, we find that FC-A and a potent derivative, stabilize interactions between 14-3-3 proteins and multiple components of the Rap1 pathway to facilitate axon growth. Thus, FC-A and its derivatives exhibit remarkable polypharmacology facilitating axon regeneration. These findings show that 14-3-3 adaptor protein complexes are druggable targets and identify a new class of small molecules that may be further optimized for the repair of CNS damage.

OBJECTIVES

1. Define 14-3-3- adaptor proteins and small molecules targeting these proteins

2. Describe the influence of small molecules targeting 14-3-3 proteins on axon regeneration in a pre-clinical optic nerve injury model

3. Discuss the mechanism used by these small molecules to promote axon regeneration

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