University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Master of Science

of

LENA CHEN

BSc (University of Ottawa, 2015)

"Ankyrin-B: Proteostasis and Implications on Cellular Behaviours"

Division of Medical Sciences

Thursday, April 26, 2018
10:30 A.M.
Human and Social Development Building
Room A270

Supervisory Committee:
Dr. Leigh Anne Swayne, Division of Medical Sciences, University of Victoria (Co-Supervisor)
Dr. Laura Arbour, Division of Medical Sciences, University of Victoria (Co-Supervisor)
Dr. Raad Nashmi, Division of Medical Sciences, UVic (Member)
Dr. Chris Nelson, Department of Biochemistry and Microbiology, UVic (Outside Member)

External Examiner:
Dr. Bob Chow, Department of Biology, UVic

Chair of Oral Examination:
Dr. Fayez Gebali, Department of Electrical and Computer Engineering, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

Ankyrin-B (Ank-B) is a crucial scaffolding protein regulating expression and localization of contractile machinery in the cardiac muscle. Ank-B associates with its binding partners through its membrane-binding domain (MBD) but the role of the MBD in regulating the stability of Ank-B itself is unknown. Recent genetic investigations in the First Nations Community, the Gitxsan of Northern BC, identified a mutation in Ank-B (p.S646F c.1937 C>T) associated with a cardiac arrhythmia, Long QT Syndrome Type 4 (LQTS4). Distinct from other LQTS4 subtypes, individuals with the p.S646F variant exhibit development deficits including cardiomyopathies and accessory electrical pathways. How p.S646F interferes with the development of the heart is unknown due to a fundamental lack of understanding regarding to Ank-B proteostasis and its role in cardiac differentiation. Using *in vitro* techniques, I determine the rate Ank-B is degraded, and the primary mechanism of degradation: the proteasome. I further hypothesize that p.S646F interferes with Ank-B proteostasis, thereby affecting cardiomyocyte behaviours. To further understand the role of the MBD particularly, I utilize the p.S646F variant to determine the importance of the MBD in Ank-B proteostasis and the resulting implications. I show that p.S646F destabilizes Ank-B in cardiomyoblasts, due to increased degradation via the proteasome. Furthermore, overexpression of p.S646F Ank-B had a significant impact on cellular behaviours including reducing cell viability, decreasing cell proliferation rates, and altering expression of cellular differentiation markers. Together these data address critical knowledge gaps with regards to Ank-B protein homeostasis and the role of Ank-B in cardiomyocyte viability and development. These findings inform the diagnosis and treatment of patients with the p.S646F variant, creating potential targeted pathways of intervention, and furthering our understanding of the role of the Ank-B in the development of the heart.