University of Victoria | Graduate Studies

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

of

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BSc (University of Tulsa, 2013)

"STAT3 Regulation of Citrate Synthase is Essential During the Initiation of Cell Growth"

Department of Biochemistry and Microbiology

Monday, July 25, 2016
9:30 A.M.
Engineering and Computer Science Building
Room 130

Supervisory Committee:
Dr. Julian Lum, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Caren Helbing, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Patrick Walter, Department of Biology, UVic (Outside Member)

External Examiner:
Dr. Juergen Ehlting, Department of Biology, UVic

Chair of Oral Examination:
Dr. Peter Wan, Department of Chemistry, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

To exit a non-proliferative state and enter cell division, metazoan cells require external signals to facilitate activation and metabolic reprogramming. As cell growth is required before cell division, cells redirect their metabolism for *de novo* synthesis of cell building blocks, including phospholipids for cell membrane construction. How cells coordinate initial signaling events with metabolism is unknown. Lineage-specific factors transmit activating signals via cell surface receptor-ligand interactions. Among these are PI3K/AKT, MAP/ERK, and JAK/STAT, all of which have been described to contribute to metabolic regulation. In particular, the signal transducer and activator of transcription (STAT) is a transcription factor with broad roles in cell cycle progression and glucose metabolism. Previous data from our laboratory found that one STAT family member, STAT3, was one of the primary signaling pathways activated when transitioning out of a resting state. Inhibition of STAT3 was found to suppress the initiation of cell growth and citrate levels, a main intermediate for fatty acid synthesis, suggesting a connection to cell metabolism. This thesis investigates the role of STAT3 in the regulation of metabolism in cells transitioning from a resting state to a cell growth state.

The first chapter of this thesis provides relevant background information on the metabolic and signaling pathways involved in a resting and cell growth state. It also provides data that supports an important role for STAT3 during initial cell growth. The second chapter demonstrates the importance of STAT3 in multiple cell types using a small molecule inhibitor of STAT3, STAT3 knockdown, and knockout experiments. I also establish a potential link between STAT3 and the metabolic enzyme citrate synthase (CS) for the synthesis of citrate. In the third chapter I show that STAT3 transcriptionally regulates CS through two binding sites, CS1 and CS2. Finally, I determine that CS is essential for initial cell growth and that exogenous citrate can rescue the loss in cell growth and proliferation observed in the CS and STAT3 knockdown cells. Together, these findings describe a novel mechanism for initial cell growth whereby signaling and metabolic events are tightly linked to regulate the transition from a resting state to a state of initial cell growth. These results may uncover new strategies to block the initiation of proliferation in human pathological conditions including tumor recurrence and autoimmunity.