UNIVERSITY of GUELPH

COLLEGE of BIOLOGICAL SCIENCE

DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY

Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of ***Doctor of Philosophy*** *of*

BRANDON SMITH

on Wednesday, May 11, 2022 at 9:30 a.m. (online)

Thesis Title: **CREB3/LUMAN as a novel regulator of energy metabolism**

Examination Committee:

Dr. John Vessey, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Marica Bakovic, Dept. of Human Health and Nutritional Sciences
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Joseph Yankulov, Dept. of Molecular and Cellular Biology
Dr. René Jacobs, Dept. of Agricultural, Food and Nutritional Science, University of Alberta (External Examiner)

Advisory Committee:
Dr. Ray Lu (Co-Advisor)
Dr. Marica Bakovic (Co-Advisor)
Dr. Jim Uniacke

Abstract: CREB3 is a cellular stress-associated protein with much of its physiological and cellular functions remain to be elucidated. Stress-associated proteins have been previously well established as metabolic regulators and protect cells from toxic levels of reactive oxygen species (ROS). This thesis investigated a novel role of CREB3 in regulating energy metabolism by utilizing *Creb3*-deficient mice and mouse embryonic fibroblast (MEF) cells. It was found that *Creb3*-deficient mice had an increase in energy expenditure with no differences in energy intake. This resulted in the protection from high-fat diet-induced weight gain, hyperglycemia, and sex-specific tissue lipid accumulation in *Creb3*-deficient mice. *Creb3*-deficient males in particular were protected from hepatic accumulation of lipids and resisted high-fat diet-induced glucose intolerance while *Creb3*-deficient females were protected from lipid accumulation in skeletal muscle. These results suggest CREB3 acts as a metabolic brake, presumably under stressed conditions such as feeding on a high-fat diet. CREB3 has previously been linked to the regulation of endoplasmic reticulum (ER)-Ca2+ release which can stimulate ATP production as it enters the mitochondria. ER and mitochondrial Ca2+ homeostasis was investigated in *Creb3*-deficient MEF cells as a potential mechanism in which CREB3 controls energy metabolism. It was found that CREB3 did indeed inhibit ER-Ca2+ release although the exact mechanism of this remains unknown. Subsequently, *Creb3*-deficient MEFs had increased mitochondrial Ca2+ levels and thus drastically elevated basal mitochondrial respiration and ATP production. *Creb3*-deficient MEFs also showed an increase in basal ROS levels, while having reduced expression of ROS protection genes *Catalase* and *Sod1*. These results suggest CREB3 may provide cells protection from ROS through the upregulation of *Catalase* and *Sod1*. Since Ca2+, ATP, and ROS have an intricate mutual interplay with one another, when one is dysregulated,

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often the others are as well. This thesis established a novel role of CREB3 as a potent regulator of energy metabolism homeostasis both at the organism and cellular levels.

Curriculum Vitae: Brandon entered the University of Guelph in the Marketing Management B. Comm program. Realizing that his interests lay elsewhere, Brandon enrolled in and graduated from a 3-year Accelerated Advanced Diploma in the Biotechnology Advanced - Forensics at Fleming College. Brandon then transferred back to the University of Guelph and graduated with an Honours B.Sc in Molecular Biology and Genetics. He began his M.Sc studies in Molecular and Cellular Biology in Winter 2018 in the lab of Dr. Ray Lu. He transferred to the Ph.D program in Summer 2019.

Publications: **Accepted by International Journal of Obesity - Nature:** Smith BS, De Silva KD, Hashemi A, Duncan RE, Grapentine S, Bakovic M, Lu R. Transcription factor CREB3 is a potent regulator of high-fat diet-induced obesity and energy metabolism. *Int J Obes*. 2022.