P.I.'S BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Ahmed Bettaieb	Assistant Professor Department of Nutrition University of Tennessee-Knoxville

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Faculty of Center, Monastir, Tunisia	B.Sc.	06/2001	Reproductive Biology
University of Quebec at Montreal, Montreal, Canada	M.Sc.	01/2004	Cancer
University of Quebec at Montreal, Montreal, Canada	Ph.D.	01/2009	Cancer
University of California-Davis, Davis, CA, USA	Post-doc	01/2009-12/2011	Obesity, Diabetes, Cancer and Cardiovascular diseases.

A. Personal Statement

Since beginning my research career, I have been devoted to building a thorough and comprehensive research portfolio in translational biological research. My research program focuses on understanding the molecular and genetic mechanisms contributing to the development of metabolic diseases including obesity, diabetes, chronic inflammation, and cardiovascular diseases. My main goal is to develop translational research plans to improve the treatment and/or prevention of these diseases. Over the past five years I have been very productive as I published in prominent peer-reviewed scientific journals (33 publications) including the Proceedings of the National Academy of Sciences, Endocrinology, the Journal of Biological Chemistry, and Gastroenterology. Additionally, during my training at UC Davis (UCD), I was able to establish several strong collaborative relationships. These collaborations were deeply gratifying and fascinating as they allowed me to learn novel experimental techniques and expand my knowledge base in the pathophysiology of chronic metabolic disorders. Also, they exposed me to the research endeavors of other investigators in the Division of Endocrinology, Immunology, Oncology, Clinical Nutrition, and Vascular Medicine at the UCD-medical center (UCDMC), Cornell University, McGill University, and Harvard Medical School.

The University of Tennessee, Knoxville (UT) has strong research efforts in the field of metabolic regulation with a number of very active groups spread across campus performing exciting research. One element that was helpful in choosing UT was the strong collaborative nature of research between laboratories and the free sharing of ideas and tools among laboratories. In addition, my interest in modulation of metabolic disorders and cardiovascular disease using dietary interventions, alongside other approaches, were the major factors that contributed to my decision to conduct my research at the UT Department of Nutrition. Further, I enjoy teaching and mentoring students, and pursuing a career in academia will give me the opportunity to engage students and fulfill my passion for teaching.

Bettaieb, A., J. Bakke, et al. (2013). "Protein tyrosine phosphatase 1B regulates pyruvate kinase M2 tyrosine phosphorylation." J Biol Chem 288(24): 17360-17371.

Bettaieb, A., J. X. Jiang, et al. (2015). "Hepatocyte NADPH Oxidase 4 Regulates Stress Signaling, Fibrosis, and Insulin Sensitivity During Development of Steatohepatitis in Mice." Gastroenterology.

Bettaieb, A., S. Liu, et al. (2011). "Differential regulation of endoplasmic reticulum stress by protein tyrosine phosphatase 1B and T cell protein tyrosine phosphatase." J Biol Chem 286(11): 9225-9235.

Bettaieb, A., K. Matsuo, et al. (2012). "Protein tyrosine phosphatase 1B deficiency potentiates PERK/eIF2alpha signaling in brown adipocytes." PLoS One 7(4): e34412.

Luria, A., A. Bettaieb, et al. (2011). "Soluble epoxide hydrolase deficiency alters pancreatic islet size and improves glucose homeostasis in a model of insulin resistance." Proc Natl Acad Sci U S A 108(22): 9038-9043.

B. Positions and Honors

Positions and Employment

2014-15: Assistant Researcher , Step IV, University of California-Davis, California; USA. Department of Nutrition. Research in the field of Obesity, Diabetes, Cardiovascular diseases, Cancer development and metastasis, Nephropathy and Neuropathy. I helped plan courses related to Nutrition and Metabolic Diseases.

2012-13: Assistant Project Scientist , Step II, University of California-Davis, California; USA. Department of Nutrition. Research in the field of Obesity, Diabetes, Cardiovascular diseases, Cancer development and metastasis. I helped plan courses related to Nutrition and Metabolic Diseases.

2008-11 : Postdoctoral fellow, University of California-Davis, California; USA. Department of Nutrition. Research in the field of Obesity, Diabetes, Cardiovascular diseases, Cancer development and metastasis. I helped plan courses related to Nutrition and Metabolic Diseases.

2007-08: Research Associate Scientist. University of Quebec at Montreal- INRS-Institut Armand-Frappier, Laval, Quebec; Canada. Department of Biological Sciences. Research in the field of Cancer and drug development.

2004-08: Teaching, training and supervision of new arrival students, University of Quebec at Montreal- INRS-Institut Armand-Frappier, Laval, Quebec; Canada. Department of chemistry and Biochemistry.

2005-06: Teaching Auxiliary: University of Quebec at Montreal- INRS-Institut Armand-Frappier, Laval, Quebec; Canada. Department of chemistry and Biochemistry.

2004-05: Teaching Auxiliary: Analytical Chemistry, University of Quebec at Montreal- INRS-Institut Armand-Frappier, Laval, Quebec; Canada. Department of chemistry.

2000-01: Research Associate Scientist. Hospital Farhat Hached, Sousse Tunisia. Research in the field of Reproductive Biology.

Other Experience

2011-Current: Reviewer for Food & Function journal, PLOS ONE, Nutrition Research, Metallomics, Diabetes, Obesity and Metabolism, In Vitro Cellular & Developmental Biology - Animal

Honors

2007: Recipient of Second place prize for best poster presentation during the 5th Oxidative Stress Consortium.

2007: Scholarship offered by the Ministère de l'Éducation du Québec (MEQ). Two years duration.

2007: Recipient of First place prize for best poster presentation during the spring conference and day of research in University of Montreal.

2007: Scholarship of Excellence Award offered by Faculty of sciences of the University of Quebec at Montreal (Funds of the department of biological sciences).

2006: Scholarship of Excellence Award offered by the Ministère de l'Éducation du Québec.

2005: Scholarship of Excellence Award offered by the foundation of UQAM, Montreal.

2005: Scholarship of Excellence Award offered by Faculty of Sciences of the University of Quebec

2004: Scholarship of Excellence Award offered by the foundation of the University of Quebec.

2002: International Research Scholarship award (IRSA) offered by the ministry for the higher education of Tunisia: five year duration.

C. Contributions to Science

My research activities while pursuing my Ph.D. were focused on trying to uncover the molecular mechanism and cellular signaling of cancer cells death in response to noninvasive biological methods, such as hyperthermia. Our promising observations led to several quantitative experimental studies and increased our understanding of the biological effects of lethal hyperthermia as well as the adaptive survival responses (thermotolerance). As a first and main author, my findings were essential in uncovering ER stress as a potential molecular mechanism through which hyperthermia can cause cancer cells death. In this regard, hyperthermia could be useful in cancer therapy through regulating ER stress pathways in tumour cells.

1. Bettaieb A and Averill-Bates DA (2005) Thermotolerance induced at a mild temperature of 40 degrees C protects cells against heat shock-induced apoptosis. J Cell Physiol 205(1): 47-57.

2. Bettaieb A and Averill-Bates DA (2008) Thermotolerance induced at a fever temperature of 40 degrees C protects cells against hyperthermia-induced apoptosis mediated by death receptor signalling. Biochem Cell Biol 86(6): 521-538.
3. Bettaieb A and Averill-Bates DA (2015) Thermotolerance induced at a mild temperature of 40 degrees C alleviates heat shock-induced ER stress and apoptosis in HeLa cells. Biochimica et biophysica acta 1853(1): 52-62.
4. Glory A, Bettaieb A and Averill-Bates DA (2014) Mild thermotolerance induced at 40 degrees C protects cells against hyperthermia-induced pro-apoptotic changes in Bcl-2 family proteins. International journal of hyperthermia: the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 30(7): 502-512.

Additionally, in collaboration with colleagues at the University of Quebec at Montreal, I uncovered novel mechanisms of toxicity for acrolein, an environmental pollutant and a lipid peroxidation product that has been shown to be involved in the pathogenesis of several diseases such as asthma, chronic obstructive pulmonary disease, cancer, atherosclerosis, Alzheimer's disease, and diabetes. My contributions were essential in uncovering the molecular mechanisms of acrolein toxicity (see list of publications).

My tenure at University of California-Davis was very productive. I achieved several breakthroughs that enhanced our understanding of metabolic regulation that are summarized below.

Role of PTP1B and its substrates in metabolic regulation. Using combined biochemical, molecular, and mass spectroscopy approaches, I identified new physiological substrates for PTP1B in the adipose and pancreas tissues and provided new mechanistic and functional insights into the role of PTP1B in obesity, Type 2 diabetes, and acute pancreatitis.

Role of SHP2 and TCPTP in metabolic regulation. I addressed the physiological role of hepatic Shp2 using liver-specific deletion [1, 2]. With a team of collaborators, I demonstrated that liver-specific Shp2 deficient mice gained less weight and exhibited increased energy expenditure compared with controls. In addition, hepatic Shp2 deficiency led to decreased liver steatosis and prevented the development of insulin resistance following high fat feeding. These studies identified hepatic Shp2 as a novel regulator of systemic energy balance. In addition, I investigated the endocrine and exocrine functions of TCPTP using pancreas-specific deletion. We demonstrated that pancreatic TCPTP deficiency mitigated acute pancreatitis in mice [3] and affected pancreatic beta cell function and insulin secretion [4].

Role of sEH in metabolic regulation, pain sensation, and acute pancreatitis. sEH deficiency and inhibition have beneficial effects in cardiovascular, renal, and inflammatory diseases in murine models, but the precise role of sEH in glucose homeostasis and the underlying molecular mechanism remain largely unexplored. In collaboration with Dr. B. Hammock (UCD) I addressed this using genetic, pharmacological, biochemical, and metabolomic approaches. In a series of studies, my contribution helped demonstrate that sEH deficiency and pharmacological inhibition improves glucose tolerance [5], reduces pain-related behavior [6] (Bettaieb et al., submitted *Proceedings of the National Academy of Sciences*), regulates endoplasmic reticulum stress [7] and fibrosis (Harris et al., submitted *American Journal of Physiology*), and attenuates acute pancreatitis (Bettaieb et al., submitted PLoS One). Collectively, these studies provided new insights into sEH metabolic functions and the molecular mechanisms mediating its actions. Importantly, attenuation of pain by sEH pharmacological inhibition is being tested for human therapeutic intervention and initial results are promising.

Nutritional, pharmacological, and surgical approaches to improve the metabolic state. Diet can play a significant role in preventing the metabolic syndrome and its associated pathologies. In collaboration with Dr. P. Oteiza (UCD) I investigated the effects of flavan-3-ol (−)-epicatechin (EC), the most abundant flavonoid in the human diet, on metabolic regulation. I demonstrated that EC prevented TNFa-induced activation of signaling cascades that led to inflammation and insulin resistance in adipocytes [8, 9]. Further, EC mitigated high fructose-induced insulin resistance in a rat model by modulating redox signaling and ER stress response adipocytes [8].

5. Matsuo, K., et al., Altered glucose homeostasis in mice with liver-specific deletion of Src homology phosphatase 2. J Biol Chem, 2010. 285(51): p. 39750-8.
6. Nagata, N., et al., Hepatic Src homology phosphatase 2 regulates energy balance in mice. Endocrinology, 2012. 153(7): p. 3158-69.
7. Bettaieb, A., et al., Pancreatic T cell protein-tyrosine phosphatase deficiency ameliorates cerulein-induced acute pancreatitis. Cell Commun Signal, 2014. 12: p. 13.

8. Xi, Y.L., S. ; Bettaieb, A.; K. Matsuo; I Matsuo; E. Hosein; S. Chahed; F. Wiede; S. Zhang; Z.Y. Zhang; R. N. Kulkarni; T. Tiganis; F. G. Haj. , Pancreatic T cell protein-tyrosine phosphatase deficiency affects beta cell function. Diabetologia, 2014.
9. Luria, A., et al., Soluble epoxide hydrolase deficiency alters pancreatic islet size and improves glucose homeostasis in a model of insulin resistance. Proc Natl Acad Sci U S A, 2011. 108(22): p. 9038-43.
10. Inceoglu, B., et al., Acute augmentation of epoxygenated fatty acid levels rapidly reduces pain-related behavior in a rat model of type I diabetes. Proc Natl Acad Sci U S A, 2012. 109(28): p. 11390-5.
11. Bettaieb, A., et al., Soluble epoxide hydrolase deficiency or inhibition attenuates diet-induced endoplasmic reticulum stress in liver and adipose tissue. J Biol Chem, 2013. 288(20): p. 14189-99.
12. Bettaieb, A., et al., (-)-Epicatechin mitigates high-fructose-associated insulin resistance by modulating redox signaling and endoplasmic reticulum stress. Free Radic Biol Med, 2014. 72: p. 247-56.
13. Vazquez-Prieto, M.A., et al., (-)-Epicatechin prevents TNFalpha-induced activation of signaling cascades involved in inflammation and insulin sensitivity in 3T3-L1 adipocytes. Arch Biochem Biophys, 2012. 527(2): p. 113-8.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1tqnubbtilvQa/bibliograpahy/47948936/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

NIH-K99-R00 National Institute of Health (Bettaieb, A) 9/01/2013– 8/31/2018

Metabolic functions of adipose pyruvate kinase M2

The major goal of this project is to determine the physiological roles of PKM2 in adipose tissue.