TACSM Abstract

C.elegans as a Diabetes & Ischemia Model: Identification of Genetic and Cellular Changes that Modulate the Survival of Hyperglycemia and Oxygen-Deprivation

Garcia AM, Ladage ML, McFarlin BK, Azad RK, & Padilla PA

Department of Biological Sciences; University of North Texas; Denton, TX

Category: Doctoral

Advisor / Mentor: Padilla, Pamela (Pamela.Padilla@UNT.edu)

ABSTRACT

Diet represents an exogenous influence that often yields colossal effects on an individual's phenotype, physiology, long-term health and disease risk. The overconsumption of dietary sugars for example, has contributed to significant increases in obesity and type 2 diabetes, health issues that are costly both in terms of dollars and human life. Additionally, individuals with these conditions have compromised oxygen delivery and thus, an increased vulnerability to other oxygen-deprivation related disease states, including cardiovascular disease, ischemic strokes, vascular and coronary diseases and myocardial infarction. While human and other mammalian studies have shown that individuals with type 2 diabetes have a worse prognosis and recovery after being challenged with an oxygen-deprivation related injury, mechanistic understanding regarding why this is the case is lacking. We are using *C. elegans* to identify genetic and cellular changes that modulate responses to the combinatory stress of hyperglycemia and oxygen-deprivation. We have determined that *C. elegans* fed a high glucose diet have increased cellular glucose (hyperglycemia), increased lipid content and increased sensitivity to oxygen-deprivation (anoxia) and ROS induction. We have determined that the insulin-like signaling pathway, via fatty acid and ceramide synthesis, modulates the increased sensitivity to anoxia. In mammalian systems, specific ceramide species increase after an ischemic event and are also linked to detrimental effects observed in diabetic patients, underscoring the potential role these molecules have in modulating oxygen-deprivation and hyperglycemia responses in individuals. Specific fatty acids also have known roles as both signaling molecules and as integral membrane components, thus, we hypothesize that a high-glucose diet disrupts fatty acid and ceramide homeostasis resulting in aberrations in metabolic processes and stress response pathways that are essential for the survival of oxygen-deprivation. Additionally, gene expression analysis (via RNAseq) on *C. elegans* fed either a standard or glucose-supplemented diet revealed that glucose impacts the expression of genes involved with multiple cellular processes, including lipid and carbohydrate metabolism, stress responses, cell division and extracellular functions. Several of the genes we identified are also differentially regulated in obese and type-2 diabetic human individuals, indicating a high degree of conserved gene expression changes between *C. elegans* fed a glucose-supplemented diet and in diabetic and/or obese human individuals. Together this work underscores how both diet and

genotype impact stress responses and supports the use of *C. elegans* as a model for further elucidating the molecular mechanisms regulating dietary-induced metabolic diseases.