Research Statement:

Chronic diseases (e.g. heart disease, cancer, and diabetes) are among the leading causes of death and disability in the United States. Both environment and genetics (e.g. diet and genotype) are contributing factors for the development/progression of chronic diseases in humans. Type 2 diabetes (T2D), for example, has various metabolic abnormalities including insulin resistance, hyperglycemia, and increase in free fatty acids that contribute to vascular system malfunction. Hyperglycemia impacts the vascular system by affecting O_2 delivery to organs which ultimately lead to organ dysfunction, amputations, and blindness. Type 2 diabetes is a complex disease, and the effects hyperglycemia has on whole animal gene expression is not well understood. In addition, such gene expression changes involved in O_2 deprivation responses remain to be studied.

Our previous studies reveal that a glucose-supplemented diet impacted the gene expression of 2,370 genes involved in various biological processes such as metabolism, cellular process, localization, development, immune response, biological regulation, response to stimulus, and reproduction. We also showed that a sugar-supplemented diet (i.e. glucose) induced O_2 deprivation sensitivity. The genetic model organism *C. elegans* is used to understand the consequences a glucose diet has on animal physiology and stress responses (O_2 deprivation). Our ***objective*** is to identify how a glucose-supplemented diet, independently, impacts gene expression and metabolic processes which in-turn compromise O_2 deprivation responses. I am using molecular, genetic, transcriptomic, metabolomics, and bioinformatic analysis to investigate the impact a glucose-diet has on *C. elegans* and if such changes impact O_2 deprivation responses. The ***rationale and relevance*** for our studies are that humans with T2D experience a compromised oxygen delivery system, and the underlying mechanisms are not yet understood. Current approaches to minimize the negative impacts a high-glucose diet has on O_2 deprivation responses is limited. By using *C. elegans* as a model system, we can progress from understanding the glucose-diet induced molecular changes to identifying mechanisms that induce O_2 deprivation responses. I ***hypothesize*** that a glucose-supplemented diet induces gene expression and metabolite changes that compromise O_2 deprivation survival. We test this hypothesis with the following specific aims:

Aim 1: Identify gene expression regulators that are induced by a glucose-supplemented diet using the *acs-2::*GFP reporter and examine if these regulators impact O_2 deprivation responses. The gene expression changes in animals supplemented with glucose, relative to standard diet, identified 2,370 genes (1,850 up-regulated, 520 down-regulated). Among the up-regulated transcripts, several available GFP reporters were examined and *acs-2::*GFP was identified as a glucose diet responsive marker. Genetic and cellular approaches will be used to identify gene regulators that regulate *acs-2* in a glucose-supplemented diet. Furthermore, the gene regulators will be used to test if signaling pathways impacting O_2 deprivation responses can be uncovered.

Aim 2: Investigate if a glucose-supplemented diet impacts the metabolite profile, using targeted metabolomics, and assess if these changes impact O_2 deprivation responses. The power of using *C. elegans* as a model organism is that we can use large whole organismal populations to identify the metabolic state of single metabolites due to diet. We use a metabolomics approach to identify single metabolite (e.g. metabolites involved in sugar metabolism) differences between animals raised in a glucose-supplemented diet and animals raised on a standard diet.

The human homologs for *C. elegans* gene regulators identified to be relevant for O_2 deprivation responses will be examined to determine if they have been implicated in obesity, diabetes or metabolic disorders. Given the degree of conservation in genes between metazoans and higher order organisms, accomplishing these aims could translate into a greater understanding of the molecular changes that occur in individuals with T2D.