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As an undergraduate student, I always had an interest in doing scientific research and was very fortunate to have the opportunity do so twice as a summer student and in my fourth year for my honors research project. These experiences reinforced my desire to pursue a career in research. After obtaining my B.Sc Honors degree in Biochemistry at the U of A, I continued my studies and pursued a Ph.D. under the supervision of Dr. Bernard Lemire in the Department of Biochemistry. One of the main focuses of the lab centers on elucidating the structure, function and assembly of the enzyme succinate dehydrogenase (SDH). SDH participates in two essential metabolic pathways, the mitochondrial respiratory chain and the Krebs cycle. As a result, deleterious mutations that inhibit SDH enzyme function can produce severe physiological consequences resulting in a wide variety of clinical presentations such as neurodegenerative disorders and cancers. This diverse range of diseases highlights the genotype/phenotype complexity associated with SDH dysfunction which is still poorly understood. My Ph.D. thesis research focused on elucidating the role of chaperones in the biogenesis of this complex enzyme and molecular mechanism of oncogenesis associated with SDH dysfunction. I examined these issues using yeast as a model system and a variety of biochemical, molecular biological and genetic techniques.

After completing my work in the Lemire lab, I was given the opportunity to expand my areas of expertise and learn new techniques by joining the research group of Dr. Brian Sykes. The major tool of the laboratory is nuclear magnetic resonance (NMR) spectroscopy and one of the areas of research involves using NMR-based metabolomic studies to characterize and diagnose human disease. Metabolomics is an emerging area of study and is well suited for the examination of complex metabolic disorders, such as mitochondrial diseases. With excellent training provided by Dr. Sykes and assistance of my colleagues, I utilized NMR-based metabolic footprinting, in conjunction with multivariate statistical analysis, to gain insight into the underlying global metabolic consequences of SDH dysfunction in a yeast model system. This approach examines the extracellular metabolome and can provide insightful information about intracellular metabolic status due to the strong link between the two. A total of 36 metabolites were identified and quantified, demonstrating the wealth of biochemical information that can be extracted using this method. Our results indicate that several areas of yeast metabolism were highly perturbed due to the SDH mutations. Using multivariate statistical analysis we were able to discriminate of the metabolic phenotypes or metabotypes of individual mutants, including mutants that are otherwise phenotypically indistinguishable. Our findings also show that a large number of metabolites contributed significantly to the separation of the groups and demonstrates the importance of evaluating a comprehensive metabolic profile, rather than a few key metabolites. The metabotypes of the SDH mutants were also highly correlated to their growth yields, suggesting that characterization of metabotypes may offer a novel and rapid means of gaining insight into the phenotype of a new mutation.

Our study provides novel insight into the metabolic effects of SDH dysfunction and extends the application of metabolic footprinting to the examination of hypomorphic mutations. It also demonstrates the application of metabolomic analysis to complex metabolic disorders, such as mitochondrial diseases.