Elucidating the Mitochondrial Architecture of Branched Chain Amino Acid Metabolism
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Branched chain amino acid metabolism (BCAA) is based in the mitochondrial matrix and comprised of 17 enzymes, some shared, organized into three pathways to the catabolism of leucine, isoleucine, and valine (LEU, ILE, and VAL respectively). However, the physical relationships of the various enzymes in the pathways are unknown. Diseases such as isovaleric academia (IVA) and maple syrup urine disease (MSUD) are just some of the disorders caused by malfunctions in the BCAA metabolism enzymes. Today, it is estimated that approximately 250,000 people in the US suffer from IVA. In this project, we sought to learn more about the BCAA pathways and their physical interactions by analyzing proteomics and metabolic flux through the system. Using chemical crosslinking and standard proteomic techniques in tandem with stably labeled isotopes of LEU, ILE, and VAL, labeled metabolic end-products of each pathway can be quantified. Our results show an implication for an energetically favorable, metabolite-channeling BCAA super-complex. The results from these experiments will not only improve our knowledge of basic science, but can also imply previously unknown therapeutic targets. Additionally, we have discovered the end product of ILE and VAL metabolism, propionyl-CoA, has shown to be reluctant to enter the TCA cycle as previously though. These studies will impact proposed anaplerotic therapies for disorders of fatty acid oxidation and BCAA metabolism currently underway.