Final report: July 14, 2020
PI: Yong Kyung Kim
Title: PTPN2 plays a novel role in beta cells to regulate mitochondrial metabolism and beta cell survival during Type 1 diabetes (T1D) progression.

Experiments:

Aim 1. Determine the beta cell mitochondrial defects associated with deletion of PTPN2 in basal and autoimmune-mediated conditions?

I have performed metabolic analysis of PTPN2-βKO mouse islets in an age dependent manner. Analysis of 17 week old mice from control vs. PTPN2-βKO showed they had normal oxygen consumption rates and glycolysis rates under basal and glucose stimulating conditions. However, by 22 weeks of age, the PTPN2-βKO mice had reduced oxygen consumption rates. Interestingly, the 22 week old PTPN2-βKO mice also showed increased glycolysis rate upon glucose stimulation and mild glucose intolerance. These data suggest that with age, loss of PTPN2 compromises mitochondrial function in beta cells, causing the aged mutant mice to have reduced response to glucose. These data strongly suggest that PTPN2-βKO beta cells have more susceptibility to age-related conditions due to altered mitochondrial and glycolytic pathways. I am currently extending these findings to understand the role of PTPN2 in maintaining beta cell function in T1D-mimicking conditions, such as treatment with proinflammatory cytokines. Also, I am generating PTPN2-βKO mice on the NOD background using NOD.RIP-CreERT_2 and NOD.PTPN2 floxed mice.

Aim 2. Analyze changes in beta cell metabolites in basal and stress conditions.

Our analysis of mitochondrial function suggests that there are altered metabolic pathways in the PTPN2-βKO islets. To determine which steps or metabolites changes are affected by the loss of PTPN2 to alter beta cell susceptibility, we performed a phospho-proteomics analysis. These studies identified two strong candidate targets: 1) ATP-Citrate lyase (ACLY) phosphorylation and 2) malate dehydrogenase (MDH) phosphorylation. Both of candidates are rate limiting enzymes in the energy metabolism: ACLY can regulate fatty acid synthesis for beta cell proliferation and MDH can regulates the ATP production for insulin exocytosis. To validate PTPN2-induced changes in islet metabolites, I am now taking an unbiased approach to identify altered metabolites in islets isolated from 26 weeks of age control VS PTPN2-βKO.

Aim 3. Dose disruption of PTPN2 modulate human beta cell function under basal and/or autoimmune conditions?

This was a only one-year grant, so future studies will focus on determining how loss or reduction of PTPN2 in human beta cells affects metabolic functions.

In summary, I have completed the initial characterization of PTPN2-βKO mice. These studies revealed that loss of PTPN2 causes age-related defects in beta cell metabolic functions. I am currently exploring the molecular targets of PTPN2 that cause this phenotype. Future studies will assess how loss of PTPN2 affects beta cell function in type 1 diabetes mimicking conditions, in mice and humans. These studies are beginning to identify how mutations in PTPN2, a prominent T1D susceptibility gene, can compromise beta cell function during autoimmune conditions.