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Sugar, Fat, and the Implications of Glucolipotoxicity in Pancreatic Beta Cells

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Abstract: Type 2 diabetes is a problem that is ever increasing in the United States of America. According to the CDC, 1 in 10 Americans have this condition. Type 2 diabetes not only is prevalent in adults but has increasingly been found in children as time has gone on. One of the leading theories of causation for type 2 diabetes is glucolipotoxicity. Where due to overnutrition, specifically in fats and sugars in the form of fatty acids and glucose, causes cellular dysfunction within pancreatic beta cells. Pancreatic beta cells are the cells responsible for secreting insulin, initially the cell compensates by increasing its metabolism and increasing insulin expression and secretion. This allows the body to uptake glucose, however in type 2 diabetes the body becomes insensitive to insulin. As such the pancreatic beta cells increase the output of insulin, stressing the cell through the increased expression and workflow of creating and folding insulin through the endoplasmic reticulum (ER). Pancreatic beta cells also cannot forever increase their metabolism, eventually this collapses, due to glycolysis and fatty acid oxidation inhibiting each other while the cell attempts to do both. This creates metabolic stress resulting in radical oxygen species (ROS) being generated through rampant oxidative phosphorylation. Excess fatty acids existing within the cytoplasm can also react with compounds and proteins creating cascading effects leading to inhibiting crucial transcription factors, housekeeping proteins, destabilizing intracellular calcium levels, increasing ER stress, ROS production, and apoptosis. New treatments for type 2 diabetes are constantly being researched, recently lipid droplets have come into this scope of thought. These lipid droplets seem to have protective effects against lipotoxicity in pancreatic beta cells as they are to incorporate excess fatty acids within the cytoplasm into themselves by turning them into triglycerides. When looking into pancreatic sections of type 2 diabetic patients, lipid droplet quantities were lower as compared to healthy pancreatic sections. Showing these lipid droplets may have protective effects.

The aim of my project is to observe these effects within pancreatic beta cells under glucolipotoxicity. Over the course of this summer, I have analyzed the effect of glucolipotoxicity on a rat cancer pancreatic cell line (INS-1), showing that increasing levels of glucolipotoxicity and exposure causes greater cell death through an MTS assay. Utilized confocal microscopy to visualize intracellular lipids and lipid droplets within INS-1 cells exposed to varying degrees of glucolipotoxicity and solidified staining procedures. Designed primers for essential genes responsible for ROS production, ER stress indicators, crucial lipid droplet forming proteins, and markers for cellular health. Next steps for my project include analyzing gene expression over varying degrees of glucolipotoxicity, and immunostaining cells for confirmation of lipid droplet staining.