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Metabolic Alterations in the Exocrine Pancreas in Type 1 Diabetes

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Abstract:

Type 1 Diabetes (T1D) is an autoimmune disease characterized by an attack of the body's immune cells on its own pancreas, resulting in the destruction of β-cells in the islets. The endocrine portion of the pancreas, which produces and secretes hormones such as insulin and glucagon, has been widely investigated in T1D studies. However, >90% of the pancreas mass is exocrine tissue. The exocrine pancreas plays a vital role in producing and secreting digestive enzymes such as amylase, lipases, and proteases to aid digestion in the small intestine. Exocrine tissue has the capacity to produce 6-20 g of protein per day, the highest per-cell capacity in the body. Although 43-80% of T1D patients exhibit exocrine dysfunction, the role of exocrine pancreas pathophysiology in this context has yet to be fully elucidated. Because protein synthesis requires significant energy consumption (4 ATP per amino acid added), decreased digestive enzyme production may be symptomatic of metabolic deficiencies. In this study, we investigate exocrine pancreas metabolism in two mouse models of T1D: NOD.Ins2-/- (PI2KO) and NOD.Rag1-/-.AI4α/β (AI4). Pancreases were excised from the mice and perfused via the bile duct with a Krebs-Henseleit buffer containing 4 mM [U-13C]pyruvate. Upon isotopic steady-state, tissues were freeze clamped and analyzed for alterations in metabolic flux corresponding with exocrine severity. Both mouse models demonstrated evidence of increased pyruvate carboxylation, reduced oxidative metabolism, and decreased amylase production. Furthermore, these differences were partially recovered with Insulin treatment. Ultimately, our results reveal unique metabolic alterations within exocrine tissue in T1D associated with altered pyruvate handling.