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Title:

Diabetes and the metabolic rewiring of pancreatic ß-cells

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Development of Type 2 Diabetes (T2D) is characterized by gradual alteration of beta-cell function, notably its metabolism-secretion coupling. Potential beta-cell metabolic rewiring might affect different pathways, like glycolysis or mitochondria. However, such assessment remains unrealistic in vivo and poorly relevant in vitro because of the metabolic resetting of islets once in culture. In order to be as close as possible to the *in vivo* situation, we used an innovative *in situ* targeted enzymatic assay on cryopreserved human pancreatic resections of control individuals (Non-Diabetic, ND), prediabetic subjects (Impaired Glucose Tolerance, IGT), and patients with T2D; compared to diabetic mouse model (db/db mice). The *in situ* targeted NBT assay showed that islet mitochondrial SDH activity was decreased in diabetic patients with elevated HbA1c, while the glycolytic capacity was unchanged. This suggested metabolic rewiring in islets from patients with T2D, which was substantiated by the increased LDH activity accompanying elevated HbA1c levels. Overall, in situ metabolic mapping of cryopreserved pancreatic islets indicates beta-cell dedifferentiation in human subjects with poor glycemic control.

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