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Islet Inflammation: A Causal Link Between Diabetes and Pancreatic Cancer?

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Type 2 diabetes (T2DM) is characterized hyperglycemia due to impaired insulin secretion and a deficit of pancreatic beta cells in the setting of insulin resistance. Most individuals are able to compensate for insulin resistance by increasing insulin secretion so the genetic basis of T2DM appears to be linked to the underlying mechanisms leading to this abnormal pancreatic islet response to insulin resistance. In support of this, pancreatic islets in T2DM have a specific pathology. The ~65% deficit in beta cells is presumably due to increased beta cell apoptosis, the underlying mechanisms of which include a misfolded protein induced endoplasmic reticulum stress, mitochondrial dysfunction and local release of inflammatory cytokines. It has long been recognized that there is an association between T2DM and pancreatic cancer. One explanation for this is the development of diabetes in relation to pancreatic cancer, when the diagnoses are temporarily related. However there is also an increased risk of pancreatic cancer with long standing T2DM. We propose that a plausible explanation for this association is the consequence of long term exposure of surrounding pancreas to cytokines release by inflamed islets. Further, we speculate that there is a common progenitor cell niche in the pancreas for exocrine and endocrine repair, comparable to that in other gastroenterological organs, repopulating the exocrine and endocrine pancreas. Chronic inflammatory mediated stimulus of such a progenitor would be expected with time, in those with underlying relevant mutations such as KRAS activating, to increase the risk of malignant transformation.